Third Edition

Textbook of Pediatrics

As per the latest NMC Guidelines | Competency Based Medical Education (CBME) Curriculum under Graduate Medical Education Regulation

Mukesh Agrawal

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Ayush

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Preface to the Third Edition

Encouraged by the overwhelming response to the first two editions, I am delighted to present third edition of this widely acclaimed *Textbook of Pediatrics*. Present edition has been extensively revised and updated to provide state of the art information on the subject in a concise and simplified format, according to the Competency Based Medical Education Curriculum, prescribed by National Medical Commission.

Apart from being a primary resource to undergraduate students, it is also expected to benefit postgraduates and practicing pediatricians as primer for further study.

This edition includes latest guidelines (till 2023) from various national and international academic and regulatory bodies including World Health Organization, Government of India and Indian Academy of Pediatrics (IAP), including recent Standard treatment guidelines (2022) and Guidelines for parents (2022). It also covers updated information on major national health programmes from pediatric perspectives, either in corresponding chapters or in the chapter on *Social pediatrics*. Revised IMNCI Guidelines 2021 have been presented in a new and independent Chapter 29.

While India has made major strides in the field of public health during last decade, expectations have been fuelled further with setting up of many ambitious targets under national health mission to improve healthcare for children as well as control or eliminate many infectious illnesses. This edition includes authentic demographic data from latest sources, e.g. National Family Health Survey –5 (2021) and Sample Registration Survey (2022), as well as current targets set-up under national health mission/policy.

Among other noteworthy features of this edition are exclusive chapters on *History taking*, *General examination and Procedures and Equipments* to enhance clinical skills and *Pediatric Pharmacology* for ready reference. Most of the chapters on systemic pediatrics have dedicated Sections on Basic considerations, Clinical evaluation and Laboratory investigations to enhance fundamental understanding of the subject and strengthen clinical skills. Over 200 clinical images and illustrations have been updated or added to enhance the visual appeal or many new diagnostic algorithms or step-by-step approaches have been included to simplify the process of decision making.

I am extremely grateful to renowned chapter contributors for their scholarly inputs and valuable suggestions, while updating the chapters. Special thanks are also due to Dr Niranjan Shindurnikar, my close friend and mentor in the field of publication matters, as well as colleagues and residents, who provided useful inputs and some excellent images with permission to use them.

My family has always been a constant source of inner strength including my wife Reena and Daughter Paankhi, with heavenly support of my parents and son Ayush. Further, my grandson Rahil has been kind enough to permit me work undisturbed, sometimes.

Finally, I wish to place on record my special thanks to Mr Satish Kumar Jain (Chairman) for his commitment to publish this edition at earliest, along with Mr YN Arjuna, (Senior Vice-President – Publishing, Editorial and Publicity) and his team at CBS Publishers for the commendable job, specially the illustrations.

I am sure that this edition will also be widely accepted by the students and practitioners of pediatrics as a primary resource to acquire, enhance and update their knowledge. Corrections, suggestions, feedback and reviews are welcome from readers to improve further editions, which may be sent at dr_mukesh_agrawal@yahoo.co.in

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Preface to the First Edition

Over forty percent of the Indian population falls below fourteen years of age with its unique health problems, assessment approaches and interventional needs. Add another ten percent of adolescent population and the quantitative burden of pediatric health services become obvious. Further, young children need special attention not only when sick but also when healthy, for the purpose of growth monitoring, immunization, dietary advice, etc.

Care of a child is as much an art as it is the science. While Pediatrics is an established specialty at post-graduate level, the need to strengthen pediatric training in India for undergraduates has been recognized recently with inclusion of pediatrics as a separate subject in MCI curriculum.

Although many excellent textbooks on pediatrics have been published during last decade, most of them concentrate on the training at postgraduate level and often considered as too advanced for undergraduates. Present book has been written with primary objective of undergraduate training, to provide them state-of-the-art information but in a concise and simplified format. However, postgraduates, especially Diploma students, are also expected to benefit by using this source to refresh their knowledge before further reading.

I am extremely grateful to all contributors, who promptly acceded to my request and wrote their chapters with diligence, excellence and relevance within the format and space constraints of the book.

I am indeed honored that Dr YK Amdekar, the renowned pediatrician and academician, as well as Dr SN Oak, beloved Dean and Professor & Head of Pediatric surgery at my institute, readily agreed to review the book and write Forewords to this edition.

I have no words to thank Dr Niranjan Shindurnikar, my close friend and the guiding force behind this book, who introduced me to the nitty-gritty of publication matters. My sincere thanks are also due to my colleagues and well-wishers for their ideas and cooperation. A special mention is needed for Dr Milind Tullu for proofreading and Dr Nilesh Jaiswal for illustrations. Dr CT Deshmukh, Dr Uday Khopkar, Dr Sudhir Shrivastava, Dr Kumar Doosa, Dr Radha Ghildiyal, Dr Sushma Malik and some of my residents provided me some excellent clinical photographs and X-rays, with permission to use them.

My parents have been the constant source of inner strength, so also my wife Reena and kids Paankhi & Ayush, who always encouraged me to take up this challenge and bring it to logical conclusion.

Finally, I wish to place on record my appreciation for Mr Rajesh Bhalani and their staff, for prompt and skilled publications work, as well Ms Sunita Tikare for her excellent print-setting work.

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Contents

Contributors ..... *vii*
Preface to the Third Edition ..... *ix*
Preface to the First Edition ..... *xi*
Index of Competencies ..... *xxiii*

1. Child Health in India **1**

Mukesh Agrawal

1.1 Indicators of Child Health *1*
1.2. Changing Profile of Diseases *2*
1.3 Determinants of Child Health *2*
1.4 Interventional Strategies in Child Health *3*

2. Normal Growth and Development **5**

Surbhi Rathi, Priyanka Bote, Mukesh Agrawal

2.1 Determinants of Growth and Development *5*
2.2 Laws and Patterns of Growth *6*
2.3 Normal Childhood Growth *7*
2.3.1 Somatic (Anthropometric Growth *8*
2.3.2 Dental Development (Dentition) *9*
2.3.3 Skeletal Maturation *10*
2.3.4 Body Composition *10*
2.4 Growth Norms and Growth Charts *11*
2.5 Growth Assessment and Monitoring *13*
2.6 Normal Childhood Development *18*
2.6.1 General Laws (Principles) of Development *18*
2.6.2 Developmental Milestones *19*
2.7 Developmental Assessment *21*

3. Growth and Development Disorders **33**

Samir H Dalwai, Surbhi Rathi, Mukesh Agrawal

3.1 Failure to Thrive *33*
3.2 Obesity *34*
3.3 Short Stature *37*
3.4 Tall Stature *40*
3.5 Developmental Delay *41*
3.6 Intellectual Disability *43*
3.7 Learning Disorders *45*
3.8 Hearing Disorders *47*
3.9. Speech and Language Disorders *48*
3.10. Scholastic Backwardness *49*
3.11. Autistic Spectrum Disorders *50*
3.12. Attention-Deficit Hyperactivity Disorder *52*

4. Behavioral Disorders **56**

Jane JE David, Mukesh Agrawal

4.1 Fussy Infant *56*
4.2 Eating Disorders *57*
4.2.1 Picky-Eating *57*
4.2.2 Pica *58*
4.3 Elimination Disorders *58*
4.3.1 Enuresis *58*
4.3.2 Encopresis *59*
4.4 Habit Disorders *60*
4.5 Sleep Disorders *62*
4.6 Conduct Disorders *62*
4.6.1 Breath-Holding Spells *63*
4.6.2 Temper Tantrums *63*
4.7 Anxiety Disorders *63*
4.8 Psychosomatic Disorders *64*
4.9 Child Guidance Clinic *65*

5. Normal Nutrition **66**

Radha Ghildiyal, Mukesh Agrawal

5.1 Basic Considerations *66*
5.1.1 Nutritional Requirements *66*
5.1.2 Essential Nutrients *67*
5.2 Breastfeeding *69*
5.2.1 Composition of Breast Milk *69*
5.2.2 Advantages of Breastfeeding *69*
5.2.3 Physiology of Lactation *70*
5.2.4 Correct Breastfeeding Techniques and Practices *71*
5.2.5 Common Breastfeeding Problems *73*
5.2.6 Lactation Counseling *75*
5.3 Baby Friendly Hospital Initiative *76*
5.4 Alternative Infant Feeding *77*
5.4.1 Expressed Breast Milk *77*
5.4.2 Human Milk Banking *77*
5.4.3 Top Feeding *77*
5.5 Complementary Feeding *78*
5.6 Infant and Young Child Feeding Guidelines *80*
5.7 Balanced Diet *80*

5.8 Nutritional Profile of Indian Foods *81*
5.9 Nutritional Assessment *84*

6. Nutritional Disorders 86
Radha Ghildiyal, Mukesh Agrawal
6.1 Childhood Undernutrition *86*
6.1.1 Etiopathogenesis *86*
6.1.2 Clinical Spectrum *87*
6.1.3 Diagnostic Assessment *89*
6.1.4 Severe and Moderate Acute Malnutrition *91*
6.1.5 Management of Severe Acute Malnutrition *91*
6.1.6 Severe Acute Malnutrition in Infants < 6 Months *96*
6.1.7 Moderate Acute Malnutrition *97*
6.1.8 Prevention of Undernutrition *97*
6.2 Vitamin A Deficiency *98*
6.3 Vitamin B Complex Disorders *100*
6.4 Vitamin C Deficiency (Scurvy) *104*
6.5 Vitamin D Deficiency (Rickets) *105*
6.5.1 Vitamin D Deficiency Rickets *106*
6.5.2 Vitamin D Resistant Rickets *108*
6.5.3 Hypervitaminosis D *109*
6.6 Vitamin E Deficiency *109*
6.7 Vitamin K Deficiency *109*
6.8 Mineral Disorders and Trace Elements *110*
6.9 Free Radicals in Health and Disease *112*

7. Fluid and Electrolyte Balance 114
Milind S Tullu, Mukesh Agrawal
7.1 Water Homeostasis *114*
7.1.1 Physiology of Water Balance *114*
7.1.2 Edema *116*
7.1.3 Dehydration *116*
7.2 Sodium Disorders *117*
7.3 Potassium Disorders *119*
7.4 Calcium Disorders *120*
7.5 Magnesium Disorders *122*
7.6 Acid–Base Disorders *123*
7.6.1 Normal Acid–Base Regulation *123*
7.6.2 Evaluation of Acid–Base Status *124*
7.6.3 Specific Acid–Base Disorders *125*
7.7 Parenteral Fluid Therapy *127*
7.7.1 Principles of Fluid Therapy *127*
7.7.2 Fluid Therapy in Clinical Practice *128*
7.7.3 Fluid Therapy in Specific Situations *129*

8. Immunological Disorders 131
Mukesh Agrawal
8.1 Basic Considerations *131*
8.2 Immunodeficiency Disorders *135*
8.3 Opportunistic Infections *137*
8.4 Hypersensitivity Disorders *140*
8.4.1 General Concepts in Allergy *140*
8.4.2 Anaphylaxis *142*

9. Immunization 144
Mukesh Agrawal, Niranjan Shendurnikar
9.1 Basic Considerations *144*
9.1.1 Physiology of Immunization *144*
9.1.2 Determinants of Immune Response *145*
9.1.3 Immunization Agents *146*
9.2 Individual Vaccines *147*
9.2.1 Vaccines in National Immunization Schedule *147*
9.2.2 Additional Vaccines Recommended By IAP *154*
9.2.3 Vaccines for Selective Use *156*
9.2.4 Newer Vaccines *157*
9.2.5 Combination Vaccines *158*
9.3 Immunization Schedules *158*
9.3.1 National Immunization Schedule *158*
9.3.2 Indian Academy of Pediatrics Schedule *159*
9.3.3 Missed (Catch-Up) Immunization *159*
9.3.4 Adolescent Immunization *160*
9.4 Immunization in Specific Situations *160*
9.5 Immunization Programs *162*
9.5.1 Universal Immunization Program *162*
9.5.2 Mission Indradhanush *163*
9.6 Cold Chain System *164*
9.7 Adverse Events following Immunization *165*
9.8 Safe Immunization Practices *166*
9.8.1 Counseling and Vaccine Hesitancy *167*
9.8.2 Safe Immunization Practices *167*
9.8.3 Pain and Anxiety Reduction *169*
9.9 Passive Immunization *170*

10. Infections 172
Yahswant R Gabhale, Nikita Shah, Mukesh Agrawal
10.1 Fever in Children *172*
10.1.1 Basic Considerations *172*

10.1.2 Pyrexia of Unknown Origin (Prolonged Pyrexia) *174*
10.1.3 Exanthematous Fevers (Fever with Rash) *175*
10.1.4 Hemorrhagic Fevers (Fever with Petechiae/Purpura) *175*
10.1.5 Febrile Neutropenia (Fever in a Neutropenic Child) *176*
10.1.6 Drug Fever *177*
10.2 Staphylococcal Infections *178*
10.3 Streptococcal Infections *179*
10.4 Pneumococcal Infections *180*
10.5 Diphtheria *180*
10.6 Whooping Cough *182*
10.7 Enteric Fever *183*
10.8 Shigellosis *185*
10.9 *H. influenzae* B Disease *186*
10.10 Meningococcal Infections *187*
10.11 Cholera *188*
10.12 Brucellosis *189*
10.13 Childhood Tuberculosis *189*
10.14 Leprosy *201*
10.15 Tetanus *203*
10.16 Non-clostridial Anaerobic Infections *207*
10.17 Rickettsial Fevers *208*
10.18 Measles *209*
10.19 Chickenpox *212*
10.20 Mumps *213*
10.21 Acute Poliomyelitis *214*
10.22 Enteroviral Infections (Non-Polio) *217*
10.23 Dengue *218*
10.24 Herpetic Viral Infections *223*
10.24.1 Herpes Simplex *223*
10.24.2 Infectious Mononucleosis *224*
10.24.3 Cytomegalovirus Disease *224*
10.25 COVID-19 Infection *225*
10.26 Influenza *228*
10.27 Rabies *230*
10.28 Pediatric HIV Infection *232*
10.29 Leptospirosis *242*
10.30 Fungal Infections *243*
10.31 Chlamydial Infections *244*
10.32 Mycoplasma Infections *244*
10.33 Malaria *245*
10.34 Kala-azar *252*
10.35 Filariasis *253*
10.36 Intestinal Protozoal Infections *255*
10.36.1 Amebiasis *255*
10.36.2 Giardiasis *255*
10.37 Intestinal Worm Infestations *256*
10.38 Nosocomial Infections *260*

11. Genetic Disorders 264

Kshitija R Patil, Mukesh Agrawal

11.1 Basic Considerations *264*
11.2 Modes of Genetic Inheritance *265*
11.3 Chromosomal Disorders *269*
11.3.1 Down Syndrome *270*
11.3.2 Turner Syndrome *273*
11.3.3 Klinefelter Syndrome *274*
11.4. Evaluation of Genetic Disorders *275*
11.5 Management of Genetic Disorders *277*
11.5.1 Treatment of Index Case *277*
11.5.2 Genetic Counseling *278*
11.5.3 Prenatal Diagnosis *279*
11.6 Inborn Errors of Metabolism *280*
11.6.1 Disorders of Amino Acid Metabolism *281*
11.6.2 Disorders of Lipid Metabolism *285*
11.6.3 Disorders of Carbohydrate Metabolism *287*
11.6.4 Mucopolysaccharides *289*
11.6.5 Porphyria *290*

12. Newborn 292

Anitha Haribalakrishna, Jyotsna Shrivastava, Alpa Bhosale, Mukesh Agrawal

12.1 General Terminology *292*
12.2 Perinatal Health Indicators *292*
12.3 Prenatal Pediatrics *293*
12.3.1 Essential Antenatal Care *294*
12.3.2 High-risk Pregnancy *294*
12.3.3 Fetal Monitoring *294*
12.3.4 Fetal Therapy *296*
12.3.5 Multiple Pregnancy *297*
12.4 Delivery Room Care and Neonatal Resuscitation *298*
12.4.1 Essential Delivery Room Care *298*
12.4.2 Neonatal Resuscitation *299*
12.5 Examination of A Newborn *304*
12.6 Care of Normal Newborn *310*

12.7 Minor Problems in Newborns *311*
12.8 High-risk Newborn *314*
12.9 Transport of a Sick Newborn *315*
12.10 Birth Injuries *316*
12.10.1 Birth Asphyxia *316*
12.10.2 Mechanical Birth Injuries *319*
12.11 Gestation and Birth Weight Disorders *321*
12.11.1 Prematurity (Preterm-LBW) *321*
12.11.2 Intrauterine Growth Retardation *326*
12.11.3 Large for Date Babies *327*
12.11.4 Post-maturity *328*
12.12 Thermoregulation Disorders *328*
12.12.1 Hypothermia *329*
12.12.2 Kangaroo Mother Care *330*
12.12.3 Hyperthermia *331*
12.13 Respiratory Disorders in Newborn *331*
12.13.1 D/D Respiratory Distress *331*
12.13.2 Common Respiratory Problems *332*
12.14 Neonatal Jaundice *337*
12.14.1 Physiological Jaundice *337*
12.14.2 Diagnostic Approach in Neonatal Jaundice *338*
12.14.3 Unconjugated Hyperbilirubinemia *339*
12.14.4 Kernicterus *342*
12.14.5 Neonatal Cholestasis *344*
12.15 Perinatal Infections *345*
12.15.1 Superficial Neonatal Infections *345*
12.15.2 Neonatal Septicemia *347*
12.15.3 Neonatal Necrotizing Enterocolitis *348*
12.15.4 Intrauterine Infections *349*
12.16 Neonatal Seizures *354*
12.17 Hematological Disorders in Newborn *355*
12.17.1 Bleeding Neonate *355*
12.17.2 Anemia in Newborn *357*
12.17.3 Neonatal Polycythemia *358*
12.18 Metabolic Disorders in Newborn *358*
12.19 Congenital Malformations *360*

13. Adolescence and Adolescence Disorders 363

Surbhi Rathi, Mukesh Agrawal

13.1 Adolescent Growth and Development *363*
13.2 Common Health Problems in Adolescence *364*
13.3 Psychosocial Problems in Adolescence *368*
13.4 Adolescent Health Check-up *369*
13.5 Adolescent Friendly Health Services *370*

14. Gastrointestinal Disorders 372

Prachi S Karnik, Aditi Dharap, Mukesh Agrawal

14.1 Basic Considerations *372*
14.2 Clinical Evaluation of GIT Disease *373*
14.3 Laboratory Evaluation of GIT Disease *374*
14.4 Common Presentations in GIT Disease *375*
14.4.1 Dysphagia *376*
14.4.2 Vomiting *376*
14.4.3 Abdominal Pain *378*
14.4.4 Constipation *380*
14.4.5 GIT Bleeding *381*
14.4.6 Abdominal Distension *382*
14.4.7 Abdominal Mass/Lump *382*
14.5 Disorders of Oral Cavity *382*
14.5.1 Cleft Lip and Cleft Palate *382*
14.5.2 Dental Caries *383*
14.5.3 Oral Cavity Inflammations *384*
14.5.4 Tongue Disorders *385*
14.5.5 Salivary Gland Disorders *385*
14.6 Esophageal Disorders *385*
14.6.1 Tracheoesophageal Fistula *385*
14.6.2 Gastroesophageal Reflux Disease *386*
14.7 Diaphragmatic Disorders *387*
14.7.1 Congenital Diaphragmatic Hernia *387*
14.8 Gastric Disorders *389*
14.8.1 Infantile Hypertrophic Pyloric Stenosis *389*
14.9 Intestinal Malformations *391*
14.9.1 Small Bowel Malformations *391*
14.9.2 Hirschsprung's Disease *392*
14.9.3 Anorectal Malformations *394*
14.9.4 Abdominal Wall Defects *395*
14.10 Acute Diarrhea *396*
14.11 Persistent Diarrhea *401*
14.12 Malabsorption Syndromes (Chronic Diarrhea) *404*
14.13 Acute Intestinal Obstruction *409*
14.14 Acute Appendicitis *410*
14.15 Perianal Disorders *411*
14.16 Pancreatic Disorders *412*
14.17 Disorders of Gallbladder *413*
14.18 Disorders of Peritoneum *413*

15. Disorders of Hepatobiliary System 416

Aditi Dharap, Prachi S Karnik, Mukesh Agrawal

15.1 Basic Considerations *416*

15.2 Hepatomegaly *417*
15.3 Jaundice *418*
15.4 Viral Hepatitis *419*
15.5 Acute Hepatic Failure *422*
15.6 Liver Abscess *423*
15.7 Chronic Liver Disease *424*
15.8 Portal Hypertension *428*

16. Respiratory Disorders 430

Chandrahas T Deshmukh, Mukesh Agrawal

16.1 Basic Considerations *430*
16.2 Clinical Evaluation of Respiratory Disease *433*
16.3 Laboratory Investigations in Lung Disease *436*
16.4 Common Clinical Presentations *438*
16.4.1 Recurrent/Persistent Cough *438*
16.4.2 Respiratory Distress *440*
16.4.3 Stridor *440*
16.4.4 Wheezing *441*
16.5 Ear, Nose and Throat Disorders *442*
16.5.1 Nasal Disorders *443*
16.5.2 Sinusitis *445*
16.5.3 Throat Disorders *445*
16.5.4 Ear Disorders *447*
16.6 Acute Croup *449*
16.7 Acute Bronchiolitis *451*
16.8 Bronchial Asthma *452*
16.9 Pneumonia *460*
16.9.1 Infective Pneumonia *460*
16.9.2 Non-infective Pneumonia *464*
16.10 Chronic Lung Diseases *466*
16.10.1 Bronchiectasis *466*
16.10.2 Lung Abscess *467*
16.10.3 Cystic Fibrosis *468*
16.10.4 Interstitial Lung Diseases *469*
16.10.5 Congenital Lung Malformations *470*
16.11 Miscellaneous Lung Disorders *471*
16.12 Pleural Disorders *473*
16.12.1 Empyema Thoracis *473*
16.12.2 Pneumothorax *475*

17. Disorders of Cardiovascular System 477

Radha Ghildiyal, Mukesh Agrawal

17.1 Developmental Cardiology *477*
17.1.1 Development of Heart *477*
17.1.2 Fetal Circulation *478*
17.1.3 Fetal to Neonatal Transition *478*
17.1.4 Postnatal Circulation *479*
17.2 Clinical Evaluation for Cardiac Disease *480*
17.3 Investigations in Cardiac Disease *486*
17.4 Congestive Cardiac Failure *490*
17.5 Congenital Heart Disease *494*
17.5.1 General Considerations *494*
17.5.2 Acyanotic CHDS *495*
17.5.3 Cyanotic CHDS *503*
17.5.4 Diagnostic Approach in CHD *506*
17.6 Rheumatic Fever *507*
17.7 Rheumatic Heart Disease *511*
17.8 Infective Endocarditis *515*
17.9 Myocardial Disorders *516*
17.9.1 Myocarditis *516*
17.9.2 Cardiomyopathies *517*
17.10 Arrhythmia *519*
17.11 Pericarditis *522*
17.12 Childhood Hypertension *523*

18. Disorders of Central Nervous System 528

P Keerthi Kundana, Mona Gajre, Alpana Kondekar Mukesh Agrawal

18.1 Clinical Evaluation in Neurological Disease *528*
18.2 Laboratory Evaluation in CNS Disease *532*
18.3 Comatose Child *534*
18.4 Raised Intracranial Pressure *537*
18.5 Headache *539*
18.6 Seizure Disorders *540*
18.6.1 General Considerations *540*
18.6.2 Status Epilepticus *545*
18.6.3 Febrile Seizures *545*
18.6.4 Epilepsy in Childhood *547*
18.6.5 Seizure-Like Disorders (Seizure Mimics) *550*
18.7 Cerebrovascular Strokes *551*
18.8 Hemiplegia *553*
18.9 Movement Disorders *554*
18.10 Congenital CNS Malformations *557*
18.10.1 Neural Tube Defects *557*
18.10.2 Hydrocephalus *560*
18.11 Cerebral Palsy *563*
18.12 Intracranial Infections *565*
18.12.1 Bacterial Meningitis *565*

18.12.2 Tubercular Meningitis *567*
18.12.3 Viral Encephalitis *569*
18.12.4 Autoimmune Encephalitis *571*
18.12.5 Reye Syndrome *572*
18.12.6 Cerebral Malaria *572*
18.12.7 Brain Abscess *573*
18.12.8 Tuberculoma *574*
18.12.9 Neurocysticercosis *574*
18.13 Brain Tumors *575*
18.14 Neurocutaneous Syndromes *577*
18.15 Neurodegenerative Disorders *580*
18.16 Spinal Cord Disorders *583*
18.16.1 Acute Transverse Myelitis *583*
18.16.2 Spinal Cord Injuries *583*
18.16.3 Spinal Cord Malformations *584*
18.16.4 Spinal Cord Tumors *584*
18.17 Paraplegia *584*
18.18 Neuromuscular Disorders *586*
18.18.1 Anterior Horn Cell Disorders *587*
18.18.2 Peripheral Neuropathies *588*
18.18.3 Neuromuscular Junction Disorders *590*
18.18.4 Myopathies *591*
18.19 Floppy Infant *594*
18.20 Disorders of Autonomic System *595*

19. Hematological Disorders 597

Sujata Sharma, Priyashree Mukherjee, Purvi Kadakia Kutty
Mukesh Agrawal

19.1 Basic Considerations *597*
19.2 Anemia-General Concepts *599*
19.3 Physiological Anemia of Infancy *602*
19.4 Nutritional Anemia *602*
19.4.1 Iron Deficiency Anemia *602*
19.4.2 Megaloblastic Anemia *605*
19.5 Hemolytic Anemia *606*
19.5.1 Hereditary Spherocytosis *607*
19.5.2 G6PD Deficiency Anemia *608*
19.5.3 Thalassemia *609*
19.5.4 Sickle Cell Disease *612*
19.5.5 Autoimmune Hemolytic Anemia *614*
19.6 Aplastic Anemia *614*
19.7 Polycythemia *616*
19.8 Leukocyte Disorders *616*
19.9 Physiology of Hemostasis *619*
19.10 Hemorrhagic Disorders *620*
19.11 Platelet Disorders *622*
19.11.1 Immune Thrombocytopenic Purpura *622*
19.12 Coagulation Disorders *625*
19.12.1 Hemophilia *625*
19.13 Disseminated Intravascular Coagulation *627*
19.14 Hypercoagulable States *628*
19.15 Specific Therapeutic Modalities in Hematology *629*
19.15.1 Blood-product Transfusions *629*
19.15.2 Hematopoietic Stem-cell Transplantation *631*
19.15.3 Hematopoietic Growth Factors *632*
19.16 Disorders of Spleen *632*
19.16.1 Splenomegaly *632*
19.16.2 Hyposplenic States *634*
19.17 Disorders of Lymphatic System *634*

20. Oncological Disorders 637

Purvi Kadakia Kutty, Sujata Sharma, Mukesh Agrawal

20.1 Basic Considerations *637*
20.2 Leukemia *639*
20.2.1 Acute Lymphoblastic Leukemia *639*
20.2.2 Acute Myelogenous Leukemia *642*
20.2.3 Chronic Myelogenous Leukemia *643*
20.3 Lymphoma *643*
20.3.1 Hodgkin Lymphoma *643*
20.3.2 Non-Hodgkin's Lymphoma *644*
20.4 Neuroblastoma *646*
20.5 Wilms Tumor *647*
20.6 Retinoblastoma *648*
20.7 Skeletal Malignancies *648*
20.8 Soft Tissue Sarcoma *649*
20.9 Hepatic Tumors *650*
20.10 Histiocytosis *650*

21. Renal Disorders 653

Varsha D Phadke, Apurva Shah, Neha Pandey
Mukesh Agrawal

21.1 Basic Considerations *653*
21.2 Evaluation in Renal Disease *655*
21.3 Congenital Renal Malformations *658*
21.4 Hereditary Nephropathies *660*
21.5 Hematuria *660*

21.6 Glomerulonephritis *661*
21.6.1 Acute Glomerulonephritis *662*
21.6.2 Rapidly Progressive Glomerulonephritis *663*
21.6.3 Chronic Glomerulonephritis *663*
21.6.4 Hemolytic Uremic Syndrome *664*
21.6.5 Renal Vein Thrombosis *665*
21.7 Proteinuria *666*
21.8 Nephrotic Syndrome *666*
21.9 Acute Kidney Injury *671*
21.10 Chronic Kidney Disease *675*
21.11 Tubular Disorders *677*
21.11.1 Renal Tubular Acidosis *677*
21.11.2 Hereditary Tubular Disorders *679*
21.11.3 Acute Tubular Necrosis *680*
21.12 Acute Interstitial Nephritis *680*
21.13 Urinary Tract Malformations *680*
21.14 Obstructive Uropathy *683*
21.15 Urinary Tract Infections *685*
21.16 Penoscrotal Disorders *688*

22. Disorders of Endocrine System 691

Shruti A Mondkar, Mukesh Agrawal

22.1 Basic Considerations *691*
22.2 Pituitary Disorders *691*
22.2.1 Hypopituitarism *692*
22.2.2 Growth Hormone Deficiency *692*
22.2.3 Hyperpituitarism *693*
22.2.4 Diabetes Insipidus *694*
22.2.5 Syndrome of Inappropriate ADH Secretion *694*
22.3 Thyroid Disorders *695*
22.3.1 Hypothyroidism *695*
22.3.2 Goiter *697*
22.3.3 Iodine Deficiency Disorders *698*
22.3.4 Hyperthyroidism *699*
22.4 Parathyroid Disorders *699*
22.5 Adrenal Disorders *700*
22.5.1 Adrenocortical Insufficiency *701*
22.5.2 Congenital Adrenal Hyperplasia *702*
22.5.3 Addison Disease *703*
22.5.4 Cushing Syndrome *703*
22.5.5 Hyperaldosteronism *704*
22.5.6 Adrenal Sex-steroid Producing Tumours (Adrenogenital Syndrome) *705*
22.5.7 Pheochromocytoma *705*
22.6 Disorders of Sex-steroids *705*
22.6.1 Disorders of Sex Development (Ambiguous Genitalia) *706*
22.6.2 Disorders of Puberty *708*
22.7 Diabetes Mellitus *710*
22.7.1 Type I Diabetes Mellitus (T1DM) *711*
22.8 Hypoglycemia *716*

23. Disorders of Bones and Joints 719

Mukesh Agrawal

23.1 Basic Considerations *719*
23.2 Developmental Bone Disorders *719*
23.2.1 Craniofacial Malformations *720*
23.2.2 Developmental Limb Disorders *721*
23.2.3 Spinothoracic Disorders *726*
23.3 Limping Child *728*
23.4 Skeletal Dysplasia *728*
23.5 Bone and Joint Infections *731*
23.5.1 Acute Osteomyelitis *731*
23.5.2 Septic Arthritis *732*
23.5.3 Osteoarticular Tuberculosis *733*
23.6 Osteochondroses *734*
23.7 Bone Masses and Tumors *735*
23.8 Fractures in Childhood *736*

24. Rheumatic Disorders 738

Divya Ramadoss, Mukesh Agrawal

24.1 Basic Considerations *738*
24.2 Juvenile Idiopathic Arthritis *739*
24.3 Systemic Connective Tissue Disorders *743*
24.3.1 Systemic Lupus Erythematosus *743*
24.3.2 Juvenile Dermatomyositis *745*
24.3.3 Scleroderma *746*
24.4 Vasculitis Syndromes *747*
24.4.1 Henoch-Schönlein Purpura (IGA Vasculitis) *747*
24.4.2 Wegener Granulomatosis *748*
24.4.3 Kawasaki Disease *748*
24.4.4 Polyarteritis Nodosa *749*
24.4.5 Takayasu Disease *750*

25. Skin Disorders 751

Mukesh Agrawal

25.1 Basic Considerations *751*
25.2 Developmental Skin Disorders *753*
25.3 Common Skin Infections *756*

25.3.1 Bacterial Infections *756*
25.3.2 Fungal Infections *758*
25.3.3 Viral Infections *759*
25.3.4 Parasitic Infestations *759*
25.4 Pigmentary Skin Disorders *760*
25.4.1 Hyperpigmented Lesions *760*
25.4.2 Hypopigmented Lesions *761*
25.5 Maculopapular Disorders *762*
25.6 Vesiculobullous Disorders *765*
25.7 Papulosquamous Disorders *768*
25.8 Eczematous Skin Disorders *770*
25.9 Disorders of Dermis *772*
25.10 Disorders of Subcutaneous Fat *772*
25.11 Disorders of Skin Appendages *773*
25.11.1 Hair Disorders *773*
25.11.2 Sebaceous Gland Disorders *773*
25.11.3 Sweat Gland Disorders *774*
25.11.4 Nail Disorders *775*

26. Ophthalmic Disorders 776

Mukesh Agrawal

26.1 General Considerations *776*
26.2 Ocular Disorders *776*
26.2.1 Disorders of Orbit *776*
26.2.2 Disorders of Eyelids *777*
26.2.3 Disorders of Lacrimal System *778*
26.2.4 Conjunctival Disorders *778*
26.2.5 Scleral Disorders *780*
26.2.6 Corneal Disorders *780*
26.2.7 Uveal Tract Disorders *781*
26.2.8 Pupillary Disorders *782*
26.2.9 Glaucoma *782*
26.2.10 Lens Disorders *783*
26.2.11 Retinal Disorders *783*
26.2.12 Optic Nerve Disorders *785*
26.2.13 Ocular Injuries *785*
26.3 Vision Disorders *786*
26.3.1 Amaurosis (Blindness) *786*
26.3.2 Amblyopia *787*
26.3.3 Refractive Errors *787*
26.3.4 Strabismus (SQUINT) *788*
26.3.5 Nystagmus *789*

27. Critical Care 790

Sushma Save, Pritha Das, Mukesh Agrawal

27.1 Cardiopulmonary Resuscitation *790*
27.1.1 Pediatric Basic Life Support *790*
27.1.2 Transport of Sick Child *794*
27.1.3 Pediatric Advanced Life Support *795*
27.2 Acute Respiratory Failure *798*
27.3 Shock *802*
27.4 Pediatric Intensive Care *806*
27.4.1 Consensus Guidelines for PICU *806*
27.4.2 Admission Criteria for PICU *806*
27.4.3 Vascular Access in Sick Children *806*
27.4.4 Monitoring of Critically Sick Child *807*
27.4.5 Nutrition In Critically Sick Child *808*
27.4.6 Sedation and Analgesia in Intensive Care *808*
27.4.7 Prediction of Outcome (Prism Score) *809*
27.4.8 Counseling Parents of Serious/ Terminally Ill Child *809*
27.4.9 Death Criteria and Brain Death *809*
27.5 Accidents in Childhood *810*
27.5.1 Childhood Trauma *810*
27.5.2 Burns and Scalds *814*
27.5.3 Drowning and Near Drowning *815*
27.5.4 Foreign Body Accidents *816*
27.5.5 Snake Bite *817*
27.5.6 Scorpion Sting *818*
27.5.7 Heat Injuries *819*
27.6 Poisoning in Children *820*
27.6.1 General Principles of Management *820*
27.6.2 Common Specific Poisonings *823*
27.7 Sudden Infant Death Syndrome *827*

28. Social Pediatrics 829

Mukesh Agrawal

28.1 National Health Objectives *829*
28.2 Child Health Indicators in India *829*
28.3 National Health Programmes *832*
28.3.1 National Health Mission *832*
28.3.2 Reproductive, Maternal, Newborn, Child and Adolescent Health (RMNCH+A) Approach *833*
28.3.3 Integrated Child Development Services *833*
28.3.4 Rashtriya Bal Swasthya Karyakram *834*
28.3.5 Navjaat Shishu Suraksha Karyakram *835*
28.3.6 India Newborn Action Plan *835*

28.3.7 Janani Shishu Suraksha Karyakaram *835*
28.3.8 Home-based Newborn Care *836*
28.3.9 Rashtriya Kishor Swasthya Karyakram *836*
28.3.10 National Vector Borne Disease Control Programme *836*
28.3.11 Under-Fives' Clinics *837*
28.3.12 School Health Service *837*
28.4 Socially At-Risk Children *837*
28.4.1 Child Abuse and Neglect (Child Maltreatment) *838*
28.4.2 Child Labour *839*
28.4.3 Street Children *839*
28.4.4 Girl Child *839*
28.4.5 Handicapped Child *840*
28.4.6 Juvenile Delinquency *840*

29. Integrated Management of Neonatal and Childhood Illnesses 842

Mukesh Agrawal

29.1 Outpatient Management of Children from 2 Months up to 5 Years *844*
29.2 Outpatient Management of Children below 2 Months (Sick Young Infants) *847*

30. History Taking in Pediatrics 850

Mukesh Agrawal

31. General Physical Examination 856

Mukesh Agrawal

32. Procedures and Equipments 867

Mukesh Agrawal

32.1 General Principles *867*
32.2 Injection Devices and Routes *867*
32.3 Vascular Access Procedures *868*
32.4 Resuscitation Procedures and Devices *873*
32.5 Aerosol Devices and Techniques *876*
32.6 Aspiration and Biopsy Procedures *879*
32.7 Feeding Support Procedures and Devices *884*
32.8 Urinary Catheters and Drainage Devices *884*
32.9 General Monitoring Equipment *886*

33. Drugs and Medications 888

Mukesh Agrawal, Snehal Keni, Aparanta Chandra

33.1 Anti-bacterial Therapy *888*
33.2 Anti-tubercular Agents *893*
33.3 Anti-viral Agents *894*
33.4 Anti-fungal Agents *896*
33.5 Anti-malarial Agents *896*
33.6 Anti-protozoal and Anti-parasitic Agents *897*
33.7 General Medications *899*

Index *923*

Index of Competencies

As per the latest NMC Guidelines | Competency Based Medical Education (CBME) Curriculum under Graduate Medical Education Regulation

TOPIC: Normal Growth and Development		CHAPTER
PE1.1:	Define the terminologies growth and development and discuss the factors affecting normal growth and development	2.1
PE1.2:	Discuss and describe the patterns of growth in infants, children and adolescents	2.2
PE1.3:	Discuss and describe the methods of assessment of growth including use of WHO and Indian national standards. Enumerate the parameters used for assessment of physical growth in infants, children and adolescents	2.3, 2.4
PE1.4:	Perform Anthropometric measurements, document in growth charts and interpret	2.5
PE1.5:	Define development and discuss the normal developmental milestones with respect to motor, behavior, social, adaptive and language	2.6
PE1.6:	Discuss the methods of assessment of development	2.7
PE1.7:	Perform developmental assessment and interpret	2.7
TOPIC: Common Problems Related to Growth		
PE2.1:	Discuss the etiopathogenesis, clinical features and management of a child who fails to thrive	3.1
PE2.2:	Assessment of a child with failing to thrive including eliciting an appropriate history and examination	3.1
PE2.3:	Counseling a parent with failing to thrive child	3.1
PE2.4:	Discuss the etiopathogenesis, clinical features and management of a child with short stature	3.3
PE2.5:	Assessment of a child with short stature: Elicit history, perform examination, document and present	3.3
PE2.6:	Enumerate the referral criteria for growth related problems	3.3
TOPIC: Common Problems Related to Development–1 (Developmental Delay, Cerebral Palsy)		
PE3.1:	Define, enumerate and discuss the causes of developmental delay and disability including intellectual disability in children	3.5, 3.6
PE3.2:	Discuss the approach to a child with developmental delay	3.5
PE3.3:	Assessment of a child with developmental delay–Elicit document and present history	3.5
PE3.4:	Counsel a parent of a child with developmental delay	3.5
PE3.5:	Discuss the role of the child developmental unit in management of developmental delay	3.5
PE3.6:	Discuss the referral criteria for children with developmental delay	3.5
PE3.7:	Visit a child developmental unit and observe its functioning	3.5
PE3.8:	Discuss the etiopathogenesis, clinical presentation and multi-disciplinary approach in the management of cerebral palsy	18.11
TOPIC: Common Problems Related to Development–2 (Scholastic Backwardness, Learning Disabilities, Autism, ADHD)		
PE4.1:	Discuss the causes and approach to a child with scholastic backwardness	3.10
PE4.2:	Discuss the etiology, clinical features, diagnosis and management of a child with learning disabilities	3.7
PE4.3:	Discuss the etiology, clinical features, diagnosis and management of a child with attention deficit hyperactivity disorder (ADHD)	3.12
PE4.4:	Discuss the etiology, clinical features, diagnosis and management of a child with autism	3.11
PE4.5:	Discuss the role of child guidance clinic in children with developmental problems	4.9
PE4.6:	Visit to the child guidance clinic	–
TOPIC: Common Problems Related to Behavior		
PE5.1:	Describe the clinical features, diagnosis and management of thumb sucking	4.4
PE5.2:	Describe the clinical features, diagnosis and management of feeding problems	4.2
PE5.3:	Describe the clinical features, diagnosis and management of nail biting	4.4
PE5.4:	Describe the clinical features, diagnosis and management of breath holding spells	4.6
PE5.5:	Describe the clinical features, diagnosis and management of temper tantrums	4.6
PE5.6:	Describe the clinical features, diagnosis and management of Pica	4.2
PE5.7:	Describe the clinical features, diagnosis and management of fussy infant	4.1
PE5.8:	Discuss the etiology, clinical features and management of enuresis	4.3
PE5.9:	Discuss the etiology, clinical features and management of encopresis	4.3
PE5.10:	Discuss the role of child guidance clinic in children with behavioral problems and the referral criteria	4.9
PE5.11:	Visit to child guidance clinic and observe functioning	4.9

Contd...

Contd...

TOPIC: Adolescent Health and Common Problems Related to Adolescent Health		
PE6.1:	Define adolescence and stages of adolescence	13.1
PE6.2:	Describe the physical, physiological and psychological changes during adolescence (Puberty)	13.1
PE6.3:	Discuss the general health problems during adolescence	13.2
PE6.4:	Describe adolescent sexuality and common problems related to it	13.1, 13.3
PE6.5:	Explain the adolescent nutrition and common nutritional problems	13.2
PE6.6:	Discuss the common adolescent eating disorders (anorexia nervosa, bulimia)	13.3
PE6.7:	Describe the common mental health problems during adolescence	13.3
PE6.8:	Respecting patient privacy and maintaining confidentiality while dealing with adolescence	13.4
PE6.9:	Perform routine adolescent health check-up including eliciting history, performing examination including SMR (sexual maturity rating), growth assessments (using growth charts) and systemic exam including thyroid and breast exam and the HEADSS screening	13.4
PE6.10:	Discuss the objectives and functions of AFHS (adolescent friendly health services) and the referral criteria	13.5
PE6.11:	Visit to the adolescent clinic	-
PE6.12:	Enumerate the importance of obesity and other NCD in adolescents	13.2
PE6.13:	Enumerate the prevalence and the importance of recognition of sexual drug abuse in adolescents and children	13.3
TOPIC: To Promote and Support Optimal Breastfeeding for Infants		
PE7.1:	Awareness on the cultural beliefs and practices of breastfeeding	5.2
PE7.2:	Explain the physiology of lactation	5.2
PE7.3:	Describe the composition and types of breast milk and discuss the differences between cow's milk and human milk	5.2
PE7.4:	Discuss the advantages of breast milk	5.2
PE7.5:	Observe the correct technique of breastfeeding and distinguish right from wrong techniques	5.2
PE7.6:	Enumerate the baby friendly hospital initiatives	5.3
PE7.7:	Perform breast examination and identify common problems during lactation such as retracted nipples, cracked nipples, breast engorgement, breast abscess	5.2 5.2
PE7.8:	Educate mothers on ante natal breast care and prepare mothers for lactation	5.2
PE7.9:	Educate and counsel mothers for best practices in breastfeeding	5.2
PE7.10:	Respects patient privacy	5.2
PE7.11:	Participate in breastfeeding week celebration	-
TOPIC: Complementary Feeding		
PE8.1:	Define the term complementary feeding	5.5
PE8.2:	Discuss the principles, the initiation, attributes, frequency, techniques and hygiene related to complementary feeding including IYCF	5.5
PE8.3:	Enumerate the common complimentary foods	5.5
PE8.4:	Elicit history on the complementary feeding habits	5.5
PE8.5:	Counsel and educate mothers on the best practices in complimentary feeding	5.5., 5.6
TOPIC: Normal Nutrition, Assessment and Monitoring		
PE9.1:	Describe the age related nutritional needs of infants, children and adolescents including micronutrients and vitamins	5.1
PE9.2:	Describe the tools and methods for assessment and classification of nutritional status of infants, children and adolescents	5.9
PE9.3:	Explains the calorific value of common Indian foods	5.8
PE9.4:	Elicit document and present an appropriate nutritional history and perform a dietary recall	5.9
PE9.5:	Calculate the age related calorie requirement in health and disease and identify gap	5.1
PE9.6:	Assess and classify the nutrition status of infants, children and adolescents and recognize deviations	5.9
PE9.7:	Plan an appropriate diet in health and disease	Relevant chapters
TOPIC: Provide Nutritional Support, Assessment and Monitoring for Common Nutritional Problems		
PE10.1:	Define and describe the etio-pathogenesis, classify including WHO classification, clinical features, complication and management of severe acute malnourishment (SAM) and moderate acute malnutrition (MAM)	6.1
PE10.2:	Outline the clinical approach to a child with SAM and MAM	6.1
PE10.3:	Assessment of a patient with SAM and MAM, diagnosis, classification and planning management including hospital and community based intervention, rehabilitation and prevention	6.1
PE10.4:	Identify children with under nutrition as per IMNCI criteria and plan referral	6.1, 29.1
PE10.5:	Counsel parents of children with SAM and MAM	6.1
PE10.6:	Enumerate the role of locally prepared therapeutic diets and ready to use therapeutic diets	6.1

Contd...

Contd...

TOPIC: Obesity in Children		
PE11.1:	Describe the common etiology, clinical features and management of obesity in children	3.2
PE11.2:	Discuss the risk approach for obesity and discuss the prevention strategies	3.2
PE11.3:	Assessment of a child with obesity with regard to eliciting history including physical activity, charting and dietary recall	3.2
PE11.4:	Examination including calculation of BMI, measurement of waist hip ratio, identifying external markers like acanthosis, striae, pseudogynecomastia, etc.	3.2
PE11.5:	Calculate BMI, document in BMI chart and interpret	3.2
PE11.6:	Discuss criteria for referral	3.2
TOPIC: Micronutrients in Health and Disease-1 (Vitamins ADEK, B Complex and C)		
PE12.1:	Discuss the RDA, dietary sources of Vitamin A and their role in health and disease	6.2
PE12.2:	Describe the causes, clinical features, diagnosis and management of deficiency/excess of Vitamin A	6.2
PE12.3:	Identify the clinical features of dietary deficiency/excess of Vitamin A	6.2
PE12.4:	Diagnose patients with Vitamin A deficiency, classify and plan management	6.2
PE12.5:	Discuss the Vitamin A prophylaxis program and their recommendations	6.2
PE12.6:	Discuss the RDA, dietary sources of Vitamin D and their role in health and disease	6.5
PE12.7:	Describe the causes, clinical features, diagnosis and management of deficiency/excess of Vitamin D (Rickets and hypervitaminosis D)	6.5
PE12.8:	Identify the clinical features of dietary deficiency of Vitamin D	6.5
PE12.9:	Assess patients with Vitamin D deficiency, diagnose, classify and plan management	6.5
PE12.10:	Discuss the role of screening for Vitamin D deficiency	6.5
PE12.11:	Discuss the RDA, dietary sources of Vitamin E and their role in health and disease	6.6
PE12.12:	Describe the causes, clinical features, diagnosis and management of deficiency of Vitamin E	6.6
PE12.13:	Discuss the RDA, dietary sources of Vitamin K and their role in health and disease	6.7
PE12.14:	Describe the causes, clinical features, diagnosis management and prevention of deficiency of Vitamin K	6.7
PE12.15:	Discuss the RDA, dietary sources of Vitamin B and their role in health and disease	6.3
PE12.16:	Describe the causes, clinical features, diagnosis and management of deficiency of B complex Vitamins	6.3, 19.4
PE12.17:	Identify the clinical features of Vitamin B complex deficiency	6.3, 19.4
PE12.18:	Diagnose patients with Vitamin B complex deficiency and plan management	6.3, 19.4
PE12.19:	Discuss the RDA , dietary sources of Vitamin C and their role in health and disease	6.4
PE12.20:	Describe the causes, clinical features, diagnosis and management of deficiency of Vitamin C (scurvy)	6.4
PE12.21:	Identify the clinical features of Vitamin C deficiency	6.4
TOPIC: Micronutrients in Health and Disease -2: Iron, Iodine, Calcium, Magnesium		
PE13.1:	Discuss the RDA, dietary sources of iron and their role in health and disease	19.4
PE13.2:	Describe the causes, diagnosis and management of Fe deficiency	19.4
PE13.3:	Identify the clinical features of dietary deficiency of Iron and make a diagnosis	19.4
PE13.4:	Interpret hemogram and Iron Panel	19.2, 19.4
PE13.5:	Propose a management plan for Fe deficiency anemia	19.4
PE13.6:	Discuss the National Anemia Control Programme and its recommendations	19.4
PE13.7:	Discuss the RDA, dietary sources of iodine and their role in health and disease	22.3
PE13.8:	Describe the causes, diagnosis and management of deficiency of iodine	22.3
PE13.9:	Identify the clinical features of Iodine deficiency disorders	22.3
PE13.10:	Discuss the National Goiter Control Programme and their recommendations	22.3
PE13.11:	Discuss the RDA, dietary sources of calcium and their role in health and disease	7.4
PE13.12:	Describe the causes, clinical features, diagnosis and management of Ca deficiency	7.4
PE13.13:	Discuss the RDA, dietary sources of magnesium and their role in health and disease	7.5
PE13.14:	Describe the causes, clinical features, diagnosis and management of magnesium deficiency	7.5
TOPIC: Toxic Elements and Free Radicals and Oxygen Toxicity		
PE14.1:	Discuss the risk factors, clinical features, diagnosis and management of lead poisoning	27.6
PE14.2:	Discuss the risk factors, clinical features, diagnosis and management of kerosene ingestion	27.6
PE14.3:	Discuss the risk factors, clinical features, diagnosis and management of organophosphorous poisoning	27.6
PE14.4:	Discuss the risk factors, clinical features, diagnosis and management of paracetamol poisoning	27.6
PE14.5:	Discuss the risk factors, clinical features, diagnosis and management of oxygen toxicity	27.1, 26.2

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TOPIC: Fluid and Electrolyte Balance		
PE15.1:	Discuss the fluid and electrolyte requirement in health and disease	7.1
PE15.2:	Discuss the clinical features and complications of fluid and electrolyte imbalance and outline the management	7.1-7.5
PE15.3:	Calculate the fluid and electrolyte requirement in health	7.7
PE15.4:	Interpret electrolyte report	7.2-7.5
PE15.5:	Calculate fluid and electrolyte imbalance	7.7
PE15.6:	Demonstrate the steps of inserting an IV cannula in a model	32.2
PE15.7:	Demonstrate the steps of inserting an interosseous line in a mannequin	32.2
TOPIC: Integrated Management of Neonatal and Childhood Illnesses (IMNCI) Guidelines		
PE16.1:	Explain the components of Integrated Management of Neonatal and Childhood Illnesses (IMNCI) guidelines and method of risk stratification	29.1-2
PE16.2:	Assess children <2 months using IMNCI guidelines	29.2
PE16.3:	Assess children >2 to 5 years using IMNCI guidelines and stratify risk	29.1
TOPIC: The National Health Programmes: NHM		
PE17.1:	State the vision and outline the goals, strategies and plan of action of NHM and other important national programs pertaining to maternal and child health including RMNCH A+, RBSK, RKSK, JSSK, Mission Indradhanush and ICDS	9.5, 28.3
PE17.2:	Analyse the outcomes and appraise the monitoring and evaluation of NHM	28.3
TOPIC: The National Health Programmes: RCH		
PE18.1:	List and explain the components, plan, outcome of Reproductive Child Health (RCH) Programme and appraise its monitoring and evaluation	28.3
PE18.2:	Explain preventive interventions for child survival and safe motherhood	28.3
PE18.3:	Conduct antenatal examination of women independently and apply at-risk approach in antenatal care	12.3
PE18.4:	Provide intra-natal care and conduct a normal delivery in a simulated environment	12.4
PE18.5:	Provide intra-natal care and observe the conduct of a normal delivery	12.4
PE18.6:	Perform postnatal assessment of newborn and mother, provide advice on breastfeeding, weaning and on family planning	12.5-12.6
PE18.7:	Educate and counsel caregivers of children	12.6-12.7
PE18.8:	Observe the implementation of the program by visiting the rural health centre	-
TOPIC: National Programmes, RCH - Universal Immunizations Programme		
PE19.1:	Explain the components of the Universal Immunization Programme and the National Immunization Programme	9.5
PE19.2:	Explain the epidemiology of Vaccine preventable diseases	10.4-7, 10.9-11, 10.13, 10-15, 10.18-21, 10.23, 10.25-27, 10.33
PE19.3:	Vaccine description with regard to classification of vaccines, strain used, dose, route, schedule, risks, benefits and side effects, indications and contraindications	9.2
PE19.4:	Define cold chain and discuss the methods of safe storage and handling of vaccines	9.6
PE19.5:	Discuss immunization in special situations – HIV positive children, immunodeficiency, pre-term, organ transplants, those who received blood and blood products, splenectomized children, adolescents, travellers	9.4
PE19.6:	Assess patient for fitness for immunization and prescribe an age appropriate immunization schedule	9.8
PE19.7:	Educate and counsel a patient for immunization	9.8
PE19.8:	Demonstrate willingness to participate in the national and sub-national immunization days	-
PE19.9:	Describe the components of safe vaccine practice – patient education/ Counseling; adverse events following immunization, safe injection practices, documentation and medico-legal implications	9.8
PE19.10:	Observe the handling and storing of vaccines	9.6
PE19.11:	Document immunization in an immunization record	9.8
PE19.12:	Observe the administration of UIP vaccines	9.8
PE19.13:	Demonstrate the correct administration of different vaccines in a mannequin	9.8
PE19.14:	Practice infection control measures and appropriate handling of the sharps	9.8
PE19.15:	Explain the term implied consent in immunization services	9.8
PE19.16:	Enumerate available newer vaccines and their indications including pentavalent pneumococcal, rotavirus, JE, typhoid IPV and HPV	9.2

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TOPIC: Care of the Normal Newborn, and High-risk Newborn	
PE20.1: Define the common neonatal nomenclatures including the classification and describe the characteristics of a normal term neonate and high-risk neonates	12.1, 12.5.12.8
PE20.2: Explain the care of a normal neonate	12.6
PE20.3: Perform neonatal resuscitation in a manikin	12.4
PE20.4: Assessment of a normal neonate	12.5
PE20.5: Counsel/educate mothers on the care of neonates	12.6
PE20.6: Explain the follow-up care for neonates including breastfeeding, temperature maintenance, immunization, importance of growth monitoring and red flags	12.5, 9.8, 2.5
PE20.7: Discuss the etiology, clinical features and management of birth asphyxia	12.10
PE20.8: Discuss the etiology, clinical features and management of respiratory distress in newborn including meconium aspiration and transient tachypnea of newborn	12.13
PE20.9: Discuss the etiology, clinical features and management of birth injuries	12.10
PE20.10: Discuss the etiology, clinical features and management of hemorrhagic disease of newborn	12.17
PE20.11: Discuss the clinical characteristics, complications and management of low birth weight (preterm and Small for gestation)	12.11
PE20.12: Discuss the temperature regulation in neonates, clinical features and management of neonatal hypothermia	12.12
PE20.13: Discuss the temperature regulation in neonates, clinical features and management of neonatal hypoglycemia	12.12, 12.18
PE20.14: Discuss the etiology, clinical features and management of neonatal hypocalcemia	12.18
PE20.15: Discuss the etiology, clinical features and management of neonatal seizures	12.16
PE20.16: Discuss the etiology, clinical features and management of neonatal sepsis	12.15
PE20.17: Discuss the etiology, clinical features and management of perinatal infections	12.15
PE20.18: Identify and stratify risk in a sick neonate using IMNCI guidelines	29.2
PE20.19: Discuss the etiology, clinical features and management of neonatal hyperbilirubinemia	12.14
PE20.20: Identify clinical presentations of common surgical conditions in the newborn including TEF, esophageal atresia, anal atresia, cleft lip and palate, congenital diaphragmatic hernia and causes of acute abdomen	14.5-7, 14.13
TOPIC: Genito-urinary System	
PE21.1: Enumerate the etiopathogenesis, clinical features, complications and management of urinary tract infection in children	21.15
PE21.2: Enumerate the etiopathogenesis, clinical features, complications and management of acute post-streptococcal glomerular nephritis in children	21.6
PE21.3: Discuss the approach and referral criteria to a child with proteinuria	21.7
PE21.4: Discuss the approach and referral criteria to a child with hematuria	21.5
PE21.5: Enumerate the etiopathogenesis, clinical features, complications and management of acute renal failure in children	21.9
PE21.6: Enumerate the etiopathogenesis, clinical features, complications and management of chronic renal failure in children	21.10
PE21.7: Enumerate the etiopathogenesis, clinical features, complications and management of Wilms Tumor	20.5
PE21.8: Elicit, document and present a history pertaining to diseases of the Genitourinary tract	21.2
PE21.9: Identify external markers for Kidney disease, like Failing to thrive, hypertension, pallor, Ichthyosis, anasarca	21.2
PE21.10: Analyse symptom and interpret the physical findings and arrive at an appropriate provisional/differential diagnosis	21.2
PE21.11: Perform and interpret the common analytes in a urine examination	21.2
PE21.12: Interpret report of Plain X Ray of KUB	21.2
PE21.13: Enumerate the indications for and Interpret the written report of Ultra sonogram of KUB	21.2
PE21.14: Recognize common surgical conditions of the abdomen and genitourinary system and enumerate the indications for referral including acute and subacute intestinal obstruction, appendicitis, pancreatitis, perforation intussusception, phimosis, undescended testis, chordee, hypospadias, torsion testis, hernia hydrocele, vulval Synechiae	14.9, 14.13-14 14.16, 21.16
PE21.15: Discuss and enumerate the referral criteria for children with genitourinary disorder	21.3-16
PE21.16: Counsel/educate a patient for referral appropriately	21.3-16
PE21.17: Describe the etiopathogenesis, grading, clinical features and management of hypertension in children	17.12
TOPIC: Approach to and Recognition of a Child with Possible Rheumatologic Problem	
PE22.1: Enumerate the common rheumatological problems in children. Discuss the clinical approach to recognition and referral of a child with Rheumatological problem	24.1
PE22.2: Counsel a patient with chronic illness	24.1-4
PE22.3: Describe the diagnosis and management of common vasculitic disorders including Henoch-Schönlein purpura, kawasaki disease, SLE, JIA	24.2-4

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TOPIC: Cardiovascular System–Heart Diseases		
PE23.1:	Discuss the hemodynamic changes, clinical presentation, complications and management of acyanotic heart diseases –VSD, ASD and PDA	17.5
PE23.2:	Discuss the hemodynamic changes, clinical presentation, complications and management of cyanotic heart diseases – Fallot's physiology	17.5
PE23.3:	Discuss the etiopathogenesis, clinical presentation and management of cardiac failure in infant and children	17.4
PE23.4:	Discuss the etiopathogenesis, clinical presentation and management of acute rheumatic fever in children	17.6
PE23.5:	Discuss the clinical features, complications, diagnosis, management and prevention of acute rheumatic fever	17.6
PE23.6:	Discuss the etiopathogenesis, clinical features and management of infective endocarditis in children	17.8
PE23.7:	Elicit appropriate history for a cardiac disease, analyse the symptoms, e.g. breathlessness, chest pain, tachycardia, feeding difficulty, failing to thrive, reduced urinary output, swelling, syncope, cyanotic spells, suck rest cycle, frontal swelling in infants. Document and present	17.2
PE23.8:	Identify external markers of a cardiac disease, e.g. cyanosis, clubbing, dependent edema, dental caries, arthritis, erythema rash, chorea, subcutaneous nodules, Oslers node, Janeway lesions and document	17.2
PE23.9:	Record pulse, blood pressure, temperature and respiratory rate and interpret as per the age	17.2, 31
PE23.10:	Perform independently examination of the cardiovascular system – look for precordial bulge, pulsations in the precordium, JVP and its significance in children and infants, relevance of percussion in pediatric examination, auscultation and other system examination and document	17.2
PE23.11:	Develop a treatment plan and prescribe appropriate drugs including fluids in cardiac diseases, anti-failure drugs, and inotropic agents	17.4
PE23.12:	Interpret a chest X-ray and recognize cardiomegaly	
PE23.13:	Choose and interpret blood reports in cardiac illness	17.3
PE23.14:	Interpret pediatric ECG	17.3
PE23.15:	Use the ECHO reports in management of cases	17.3
PE23.16:	Discuss the indications and limitations of cardiac catheterization	17.3
PE23.17:	Enumerate some common cardiac surgeries like BT shunt, Potts and Waterston's and corrective surgeries	17.5
PE23.18:	Demonstrate empathy while dealing with children with cardiac diseases in every patient encounter	-
TOPIC: Diarrheal Diseases and Dehydration		
PE24.1:	Discuss the etiopathogenesis, classification, clinical presentation and management of diarrheal diseases in children	14.10
PE24.2:	Discuss the classification and clinical presentation of various types of diarrheal dehydration	14.10
PE24.3:	Discuss the physiological basis of ORT, types of ORS and the composition of various types of ORS	14.10
PE24.4:	Discuss the types of fluid used in pediatric diarrheal diseases and their composition	14.10
PE24.5:	Discuss the role of antibiotics, antispasmodics, anti-secretory drugs, probiotics, anti-emetics in acute diarrheal diseases	14.10
PE24.6:	Discuss the causes, clinical presentation and management of persistent diarrhea in children	14.11
PE24.7:	Discuss the causes, clinical presentation and management of chronic diarrhea in children	14.12
PE24.8:	Discuss the causes, clinical presentation and management of dysentery in children	10.8
PE24.9:	Elicit, document and present history pertaining to diarrheal diseases	14.10
PE24.10:	Assess for signs of dehydration, document and present	14.10, 7.1
PE24.11:	Apply the IMNCI guidelines in risk stratification of children with diarrheal dehydration and refer	29.1-2
PE24.12:	Perform and interpret stool examination including hanging drop	14.3
PE24.13:	Interpret RFT and electrolyte report	21.2,7.2-5
PE24.14:	Plan fluid management as per the WHO criteria	14.10
PE24.15:	Perform NG tube insertion in a manikin	32.7
PE24.16:	Perform IV cannulation in a model	32.3
PE24.17:	Perform interosseous insertion model	32.3
TOPIC: Malabsorption		
PE25.1:	Discuss the etiopathogenesis, clinical presentation and management of malabsorption in children and its causes including celiac disease	14.12
TOPIC : Acute and Chronic Liver Diseases		
PE26.1:	Discuss the etiopathogenesis, clinical features and management of acute hepatitis in children	15.4
PE26.2:	Discuss the etiopathogenesis, clinical features and management of fulminant hepatic failure in children	15.5
PE26.3:	Discuss the etiopathogenesis, clinical features and management of chronic liver diseases in children	15.7
PE26.4:	Discuss the etiopathogenesis, clinical features and management of portal hypertension in children	15.8
PE26.5:	Elicit document and present the history related to diseases of gastrointestinal system	14.2
PE26.6:	Identify external markers for GI and liver disorders, e.g. Jaundice, pallor, gynecomastia, spider angioma, palmar erythema, ichthyosis, caput medusa, clubbing, failing to thrive, Vitamin A and D deficiency	14.2,15.2-3, 15.5, 15.7

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PE26.7:	Perform examination of the abdomen, demonstrate organomegaly, ascites, etc.	14.2
PE26.8:	Analyse symptoms and interpret physical signs to make a provisional/ differential diagnosis	14.2, 15.2-3
PE26.9:	Interpret liver function tests, viral markers, ultra sonogram report	15.1
PE26.10:	Demonstrate the technique of liver biopsy in a perform liver biopsy in a simulated environment	32.6
PE26.11:	Enumerate the indications for upper GI endoscopy	14.3
PE26.12:	Discuss the prevention of Hep B infection – universal precautions and immunization	15.4
PE26.13:	Counsel and educate patients and their family appropriately on liver diseases	15.4-8
TOPIC: Pediatric Emergencies – Common Pediatric Emergencies		
PE27.1:	List the common causes of morbidity and mortality in the under five children	1.2-3, 28.2
PE27.2:	Describe the etiopathogenesis, clinical approach and management of cardiorespiratory arrest in children	27.1
PE27.3:	Describe the etiopathogenesis of respiratory distress in children	16.4, 27.2
PE27.4:	Describe the clinical approach and management of respiratory distress in children	16.4, 27.2
PE27.5:	Describe the etiopathogenesis, clinical approach and management of shock in children	27.3
PE27.6:	Describe the etiopathogenesis, clinical approach and management of status epilepticus	18.6
PE27.7:	Describe the etiopathogenesis, clinical approach and management of an unconscious child	18.3
PE27.8:	Discuss the common types, clinical presentations and management of poisoning in children	27.6
PE27.9:	Discuss oxygen therapy, in pediatric emergencies and modes of administration	27.1, 32.4
PE27.10:	Observe the various methods of administering oxygen	24.1, 32.4
PE27.11:	Explain the need and process of triage of sick children brought to health facility	29.1-2
PE27.12:	Enumerate emergency signs and priority signs	29.1-2, 27.4
PE27.13:	List the sequential approach of assessment of emergency and priority signs	27.1.1
PE27.14:	Assess emergency signs and prioritize	27.1.1
PE27.15:	Assess airway and breathing: Recognize signs of severe respiratory distress. Check for cyanosis, severe chest indrawing, grunting	27.1-3, 16.4
PE27.16:	Assess airway and breathing. Demonstrate the method of positioning of an infant and child to open airway in a simulated environment	27.1
PE27.17:	Assess airway and breathing: Administer oxygen using correct technique and appropriate flow rate	27.1
PE27.18:	Assess airway and breathing: Perform assisted ventilation by bag and mask in a simulated environment	27.1, 32.4
PE27.19:	Check for signs of shock, i.e. pulse, blood pressure, CRT	27.3
PE27.20:	Secure an IV access in a simulated environment	32.3
PF27.21:	Choose the type of fluid and calculate the fluid requirement in shock	27.3
PE27.22:	Assess level of consciousness and provide emergency treatment to a child with convulsions/coma	
	• Position an unconscious child	18.3
	• Position a child with suspected trauma	18.3, 27.1
	• Administer IV/per rectal diazepam for a convulsing child in a simulated environment	18.6, 27.1
PE27.23:	Assess for signs of severe dehydration	7.1, 14.10
PE27.24:	Monitoring and maintaining temperature: Define hypothermia. Describe the clinical features, complications and management of hypothermia	12.12
PE27.25:	Describe the advantages and correct method of keeping an infant warm by skin to skin contact	12.12
PE27.26:	Describe the environmental measures to maintain temperature	12.12
PE27.27:	Assess for hypothermia and maintain temperature	12.12
PE27.28:	Provide BLS for children in manikin	27.1
PE27.29:	Discuss the common causes, clinical presentation, medico-legal implications of abuse	28.4
PE27.30:	Demonstrate confidentiality with regard to abuse	28.4
PE27.31:	Assess child for signs of abuse	28.4
PE27.32:	Counsel parents of dangerously ill/terminally ill child to break a bad news	27.4
PE27.33:	Obtain informed consent	32.1
PE27.34:	Willing to be a part of the ER team	-
PE27.35:	Attends to emergency calls promptly	-
TOPIC: Respiratory System		
PE28.1:	Discuss the etiopathogenesis, clinical features and management of Nasopharyngitis	16.5
PE28.2:	Discuss the etiopathogenesis of pharyngo tonsillitis	16.5
PE28.3:	Discuss the clinical features and management of pharyngo tonsillitis	16.5
PE28.4:	Discuss the etiopathogenesis, clinical features and management of acute otitis media (AOM)	16.5
PE28.5:	Discuss the etiopathogenesis, clinical features and management of epiglottitis	16.6
PE28.6:	Discuss the etiopathogenesis, clinical features and management of acute laryngo- tracheo-bronchitis	16.6
PE28.7:	Discuss the etiology, clinical features and management of Stridor in children	16.4, 16.6

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PE28.8:	Discuss the types, clinical presentation, and management of foreign body aspiration in infants and children	27.5
PE28.9:	Elicit, document and present age appropriate history of a child with upper respiratory problem including Stridor	16.4-6
PE28.10:	Perform otoscopic examination of the ear	16.5
PE28.11:	Perform throat examination using tongue depressor	16.5
PE28.12:	Perform examination of the nose	16.5
PE28.13:	Analyse the clinical symptoms and interpret physical findings and make a provisional/differential diagnosis in a child with ENT symptoms	16.5
PE28.14:	Develop a treatment plan and document appropriately in a child with upper respiratory symptoms	16.5
PE28.15:	Stratify risk in children with stridor using IMNCI guidelines	29.1
PE28.16:	Interpret blood tests relevant to upper respiratory problems	16.3
PE28.17:	Interpret X-ray of the paranasal sinuses and mastoid; and /or use written report in case of management. Interpret CXR in foreign body aspiration and lower respiratory tract infection, understand the significance of thymic shadow in pediatric chest X-rays	16.3
PE28.18:	Describe the etiopathogenesis, diagnosis, clinical features, management and prevention of lower respiratory infections including bronchiolitis, wheeze associated LRTI pneumonia and empyema	16.7, 16.9, 16.12
PE28.19:	Describe the etiopathogenesis, diagnosis, clinical features, management and prevention of asthma in children	16.8
PE28.20:	Counsel the child with asthma on the correct use of inhalers in a simulated environment	16.8, 32.5
TOPIC: Anemia and Other Hemato-oncologic Disorders in Children		
PE29.1:	Discuss the etiopathogenesis, clinical features, classification and approach to a child with anemia	19.2
PE29.2:	Discuss the etiopathogenesis, clinical features and management of iron deficiency anemia	19.4
PE29.3:	Discuss the etiopathogenesis, clinical features and management of Vit B12, Folate deficiency anemia	19.4
PE29.4:	Discuss the etiopathogenesis, clinical features and management of hemolytic anemia, thalassemia major, sickle cell anemia, hereditary spherocytosis, autoimmune hemolytic anemia and hemolytic uremic syndrome	19.5
PE29.5:	Discuss the National Anemia Control Programme	19.4
PE29.6:	Discuss the cause of thrombocytopenia in children: describe the clinical features and management of idiopathic thrombocytopenic purpura (ITP)	19.11
PE29.7:	Discuss the etiology, classification, pathogenesis and clinical features of hemophilia in children	19.12
PE29.8:	Discuss the etiology, clinical presentation and management of acute lymphoblastic leukemia in children	20.2
PE29.9:	Discuss the etiology, clinical presentation and management of lymphoma in children	20.3
PE29.10:	Elicit, document and present the history related to hematology	19.2, 19.10
PE29.11:	Identify external markers for hematological disorders, e.g. jaundice, pallor, petechiae purpura, ecchymosis, lymphadenopathy, bone tenderness, loss of weight, mucosal and large joint bleed	19.2, 19.10, 19.17
PE29.12:	Perform examination of the abdomen, demonstrate organomegaly	14.2, 15.2, 19.16
PE29.13:	Analyse symptoms and interpret physical signs to make a provisional/ differential diagnosis	19.2, 19.10
PE29.14:	Interpret CBC, LFT	19.2, 15.1
PE29.15:	Perform and interpret peripheral smear	19.2
PE29.16:	Discuss the indications for hemoglobin electrophoresis and interpret report	19.2, 19.5
PE29.17:	Demonstrate performance of bone marrow aspiration in manikin	32.6
PE29.18:	Enumerate the referral criteria for hematological conditions	19.2,4-15
PE29.19:	Counsel and educate patients about prevention and treatment of anemia	19.2,4-6
PE29.20:	Enumerate the indications for splenectomy and precautions	19.16.1
TOPIC: Systemic Pediatrics–Central Nervous System		
PE30.1:	Discuss the etiopathogenesis, clinical features , complications, management and prevention of meningitis in children	18.12
PE30.2:	Distinguish bacterial, viral and tuberculous meningitis	18.12
PE30.3:	Discuss the etiopathogenesis, classification, clinical features, complication and management of hydrocephalus in children	18.10
PE30.4:	Discuss the etiopathogenesis, classification, clinical features, and management of microcephaly in children	18.10,23.2
PE30.5:	Enumerate the neural tube defects. Discuss the causes, clinical features, types, and management of neural tube defect	18.10
PE30.6:	Discuss the etiopathogenesis, clinical features, and management of infantile hemiplegia	18.7-8
PE30.7:	Discuss the etiopathogenesis, clinical features, complications and management of febrile seizures in children	18.6
PE30.8:	Define epilepsy. Discuss the pathogenesis, clinical types, presentation and management of epilepsy in children	18.6
PE30.9:	Define status Epilepticus. Discuss the clinical presentation and management	18.6
PE30.10:	Discuss the etiopathogenesis, clinical features and management of mental retardation in children	3.6

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PE30.11: Discuss the etiopathogenesis, clinical features and management of children with cerebral palsy	18.11
PE30.12: Enumerate the causes of floppiness in an infant and discuss the clinical features, differential diagnosis and management	18.19
PE30.13: Discuss the etiopathogenesis, clinical features, management and prevention of poliomyelitis in children	10.21
PE30.14: Discuss the etiopathogenesis, clinical features and management of Duchenne muscular dystrophy	18.18
PE30.15: Discuss the etiopathogenesis, clinical features and management of ataxia in children	18.9
PE30.16: Discuss the approach to and management of a child with headache	18.5
PE30.17: Elicit document and present an age appropriate history pertaining to the CNS	18.1
PE30.18: Demonstrate the correct method for physical examination of CNS including identification of external markers. Document and present clinical findings	18.1
PE30.19: Analyse symptoms and interpret physical findings and propose a provisional /differential diagnosis	18.1, 18.3-9, 18.17, 18.19
PE30.20: Interpret and explain the findings in a CSF analysis	18.2
PE30.21: Enumerate the indication and discuss the limitations of EEG, CT, MRI	18.2
PE30.22: Interpret the reports of EEG, CT, MRI	18.2
PE30.23: Perform in a mannequin lumbar puncture. Discuss the indications, contraindication of the procedure	18.2, 32.6
TOPIC: Allergic Rhinitis, Atopic Dermatitis, Bronchial Asthma, Urticaria Angioedema	
PE31.1: Describe the etiopathogenesis, management and prevention of allergic rhinitis in children	16.5
PE31.2: Recognize the clinical signs of allergic rhinitis	16.5
PE31.3: Describe the etiopathogenesis, clinical features and management of atopic dermatitis in children	25.8
PE31.4: Identify atopic dermatitis and manage	25.8
PE31.5: Discuss the etiopathogenesis, clinical types, presentations, management and prevention of childhood asthma	16.8
PE31.6: Recognise symptoms and signs of asthma	16.8
PE31.7: Develop a treatment plan for asthma appropriate to clinical presentation and severity	16.8
PE31.8: Enumerate criteria for referral	16.8
PE31.9: Interpret CBC and CX-ray in asthma	16.8
PE31.10: Enumerate the indications for PFT	16.3, 16.8
PE31.11: Observe administration of nebulization	16.8,32.5
PE31.12: Discuss the etiopathogenesis, clinical features and complications and management of urticaria angioedema	25.5
TOPIC: Chromosomal Abnormalities	
PE32.1: Discuss the genetic basis, risk factors, complications, prenatal diagnosis, management and genetic counseling in Down's syndrome	11.3
PE32.2: Identify the clinical features of Down's syndrome	11.3
PE32.3: Interpret normal Karyotype and recognize Trisomy 21	11.3
PE32.4: Discuss the referral criteria and multidisciplinary approach to management	11.3
PE32.5: Counsel parents regarding 1. Present child 2. Risk in the next pregnancy	11.3
PE32.6: Discuss the genetic basis, risk factors, clinical features, complications, prenatal diagnosis, management and genetic Counseling in Turner's syndrome	11.3
PE32.7: Identify the clinical features of Turner syndrome	11.3
PE32.8: Interpret normal Karyotype and recognize the Turner karyotype	11.3
PE32.9: Discuss the referral criteria and multidisciplinary approach to management of Turner syndrome	11.3
PE32.10: Counsel parents regarding 1. Present child, 2. Risk in the next pregnancy	11.3
PE32.11: Discuss the genetic basis, risk factors, complications, prenatal diagnosis, management and genetic Counseling in Klinefelter syndrome	11.3
PE32.12: Identify the clinical features of Klinefelter syndrome	11.3
PE32.13: Interpret normal karyotype and recognize the klinefelter karyotype	11.3
TOPIC: Endocrinology	
PE33.1: Describe the etiopathogenesis clinical features, management of hypothyroidism in children	22.3
PE33.2: Recognize the clinical signs of hypothyroidism and refer	22.3
PE33.3: Interpret and explain neonatal thyroid screening report	22.3
PE33.4: Discuss the etiopathogenesis, clinical types, presentations, complication and management of diabetes mellitus in children	22.7
PE33.5: Interpret blood sugar reports and explain the diagnostic criteria for Type 1 Diabetes	22.7
PE33.6: Perform and interpret urine dip stick for sugar	22.7
PE33.7: Perform genital examination and recognize ambiguous genitalia and refer appropriately	22.6
PE33.8: Define precocious and delayed puberty	22.6
PE33.9: Perform sexual maturity rating (SMR) and interpret	13.1
PE33.10: Recognize precocious and delayed puberty and refer	22.6
PE33.11: Identify deviations in growth and plan appropriate referral	2.4-5

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TOPIC: Vaccine Preventable Diseases–Tuberculosis		
PE34.1:	Discuss the epidemiology, clinical features, clinical types, complications of tuberculosis in children and adolescents	10.13
PE34.2:	Discuss the various diagnostic tools for childhood tuberculosis	10.13
PE34.3:	Discuss the various regimens for management of tuberculosis as per national guidelines	10.13
PE34.4:	Discuss the preventive strategies adopted and the objectives and outcome of the National Tuberculosis Control Programme	10.13
PE34.5:	Able to elicit, document and present history of contact with tuberculosis in every patient encounter	10.13
PE34.6:	Identify a BCG scar (Photograph)	10.13, 9.2
PE34.7:	Interpret a Mantoux test	10.13
PE34.8:	Interpret a chest radiograph	10.13
PE34.9:	Interpret blood tests in the context of laboratory evidence for tuberculosis	10.13
PE34.10:	Discuss the various samples for demonstrating the organism, e.g. gastric aspirate, sputum, CSF, FNAC	10.13
PE34.11:	Perform AFB staining	10.13
PE34.12:	Enumerate the indications and discuss the limitations of methods of culturing M. tuberculi	10.13
PE34.13:	Enumerate the newer diagnostic tools for tuberculosis including BACTEC, CBNAAT and their indications	10.13
PE34.14:	Enumerate the common causes of fever and discuss the etiopathogenesis, clinical features, complications and management of fever in children	10.1
PE34.15:	Enumerate the common causes of fever and discuss the etiopathogenesis, clinical features, complications and management of child with exanthematous illness like Measles, Mumps, Rubella and Chickenpox	10.1, 10.18-20
PE34.16:	Enumerate the common causes of fever and discuss the etiopathogenesis, clinical features, complications and management of child with Diphtheria, Pertussis, Tetanus.	10.1, 10.5-6, 10.15
PE34.17:	Enumerate the common causes of fever and discuss the etiopathogenesis, clinical features, complications and management of child with typhoid	10.1, 10.7
PE34.18:	Enumerate the common causes of fever and discuss the etiopathogenesis, clinical features, complications and management of child with Dengue, Chikungunya and other vector born diseases	10.1, 10.23
PE34.19:	Enumerate the common causes of fever and discuss the etiopathogenesis, clinical features, complications and management of children with common parasitic infections, malaria, leishmaniasis, filariasis, helminthic infestations, amebiasis, giardiasis	10.1, 10.33-37
PE34.20:	Enumerate the common causes of fever and discuss the etiopathogenesis, clinical features, complications and management of child with Rickettsial diseases	10.1, 10.17
TOPIC: The Role of the Physician in the Community		
PE35.1:	Identify, discuss and defend medicolegal, socio-cultural and ethical issues as they pertain to health care in children (including parental rights and right to refuse treatment)	27.4, 28.4, 32.1

CHAPTER 1

Child Health in India

Mukesh Agrawal

Childhood is the formative period in human life, subjected to various intrinsic and extrinsic influences affecting their survival, health and disease. State of child health in a community reflects its overall socioeconomic development and health concerns.

Constitutionally, a child has been defined as an individual <18 years of age, though conventionally, pediatricians in India looks after the health of children till 12–14 years. In some countries, the scope of pediatrics extends up to 19 years, i.e. including the period of adolescence.

From the health perspectives, childhood is not a homogeneous period but includes various phases of growth and development with unique physical, mental and social health dimensions during each phase **(Table 1.1)**.

According to the Sample Registration Survey (SRS) 2022, children constitute ~24.8% of India's population, including 7.5% infants and pre-schoolers (0–4 years) and 17.3% school children (5–14 years). Another 10.2% population is adolescents in the age-group of 15–19 years.

TABLE 1.1: Various periods in childhood

Prenatal (intrauterine life or IUL)	
Ovum	0–14th day of IUL
Embryo	3rd–8th week of IUL
Fetus	9th week of IUL–till birth
Postnatal	
Neonate	0–28 days
Infant	28 days–1 year
Toddler	1–3 years
Preschool	3–5 years
School age	5 years–till onset of puberty
Adolescence	
Early adolescence	12–14 years (10–12 years in females)
Mid adolescence	14–16 years (12–14 years in females)
Late adolescence	16–18 years (14–16 years in females)

Present chapter provides an overview of current status of child health in India and its determinants as well as leading causes of morbidity and mortality and interventional strategies, while more specific aspects have been discussed in Ch 28.

1.1 INDICATORS OF CHILD HEALTH

Status of child health in a country is reflected in various morbidity and mortality indicators and their changes over a period of time.

Morbidity indicators are more reliable pointers of community health than mortality indicators. Although community data regarding patterns of childhood morbidity in India is limited due to poor reporting system, hospital data identifies three major causes of post-neonatal morbidity in Indian children—acute respiratory tract infections (~30%), acute diarrheal diseases (~20%) and other infectious disease including tuberculosis and measles (~20%), with underlying malnutrition in over 25% of these children. Many of these problems are inter-related and co-exist in the same child seeking health care.

NFHS-5 (2021) found that 7.3% and 2.8% of under-five children had history of diarrhea and respiratory infections within 2 weeks before the survey visit. It also reveals that 32.1% and 67.1% of all under-five children were underweight and anemic.

Morbidity profile is not static and keeps on changing with changes in socioeconomic and environmental status as well as health care awareness/facilities in the community. Recent years have seen substantial decline in incidence of infections and nutritional disorders, with simultaneous rise in non-infective illnesses and accidents due to changing lifestyle and other ecological factors.

Mortality indicators are relatively better defined and documented. SRS 2022 reveals that ~11.2% of all deaths in India occur during childhood, including 9.1% in infants, 0.9% in pre-schoolers (1–4 years) and 1.4% in school children (5–14 years), apart from another 1.3%

TABLE 1.2: Current mortality indicators in children	
Perinatal mortality rate (PNR)	18
Stillbirth rate (SBR)	03
Neonatal mortality rate (NMR)	20
Early NMR	15
Late NMR	05
Post-neonatal mortality rate (PNMR)	08
Infant mortality rate (IMR)	28
Under-five mortality rate (U5MR)	32

Source: SRS report 2022.

in adolescents (15–19 years). In brief, ~85% of all childhood deaths occur in first five years, ~80% in infancy, 50% in first month and 30% in first week of life.

Considering variable risk of mortality and causative factors in different age groups, many mortality indicators **(Table 1.2)** are used to assess the status of child health and efficacy of interventional programs, some of which are as follows:

Infant mortality rate (IMR), i.e. total number of deaths during first year of life compared to total number of live births in the given year, expressed as a rate per 1000 live births, is considered as the single best indicator of child health and effectiveness of health care system in a community.

According to SRS 2022, current IMR in India is 28/1000 live births (35.3 as per NFHS-5, 2021), much higher than that in developed countries (<10/1000). Within India too, IMR differs widely in urban *vs* rural population (19 *vs* 31 respectively) and from state to state - being lowest in Puducherry and Kerala, moderate in Maharashtra and highest in Bihar and Chhattisgarh (Table 28.4).

Leading causes of IMR include *neonatal problems* (53%), *pneumonia* (17%), *diarrheal disease* (5%) and other *severe infections* (4%). (SRS-COD report 2017-19)

Infancy includes two crucial phases of human life-neonatal and post-neonatal period, with diverse health problems. Sharp fall in IMR during last century (204 in 2011 to 28 in 2020) is predominantly due to decline in post-neonatal mortality after better control of exogenous factors, e.g. infection and malnutrition.

Perinatal mortality rate (PMR), i.e. total number of late fetal (>28 weeks) and early neonatal (<7 days) deaths compared to total number of live births in given year, expressed as a rate per 1000 live births, is the best indicator of care available to pregnant mother and her newborn in a given community (Ch 12.2).

According to SRS 2022, current PMR in India is 18/1000 live births, with wide geographic variations. Despite the declining trends, it is still much higher than that in most developed countries.

Neonatal mortality rate (NMR), i.e. total number of neonatal deaths <28 days of life, expressed as a rate per 1000 live births in a given year, currently stands at 20 (SRS, 2022). NMR, is mainly related to biological factors, e.g. low birth weight, birth asphyxia and congenital malformations, etc. and continues to be high in most parts of our country. Interestingly, NMR is higher in males (? biologically fragile sex).

Leading causes of NMR in India include prematurity and LBW (46%), birth asphyxia/trauma (15%), and neonatal pneumonia in 13% (SRS-COD report 2017-19).

Under-five mortality rate is a sensitive indicator of the overall development of the community, as majority of its causes, e.g. malnutrition and infection, depend on the socioeconomic status, environmental hygiene and health awareness in population. It is defined as total annual deaths <5 years of age and total live births in the same year, expressed as a rate per 1000 live births.

According to SRS 2022, current under-five mortality rate in India is 32 (41.9 as per NFHS 2021), substantially lower than 242 in 1960, due to overall socioeconomic development, easier access to health care and control of infectious diseases.

Leading causes of childhood mortality beyond infancy include injuries (21.8%), pneumonia (18%), non-communicable diseases (14%) and diarrheal diseases 13% (SRS-COD report 2017-19).

1.2 CHANGING PROFILE OF DISEASES

Etiology of childhood morbidity and mortality varies with age and may be divided into two major groups– **endogenous causes,** e.g. low birth weight, predominantly responsible for neonatal morbidity; and **exogenous causes,** e.g. infections and malnutrition, which usually affect beyond the neonatal period **(Table 1.3)**.

Trends in last three decades (1992-2020) have witnessed a sharp drop of ~67% in post-NMR (22 to 8) as compared to only 32% improvement in NMR (34 to 20). This observation suggests that improvement in these mortality indicators during recent years are largely attributable to better control of exogenous factors (dominant cause of post-NMR) than endogenous causes (dominant in newborns) are more difficult to control and need holistic strengthening of antenatal, intranatal and postnatal services.

With relative control of common illnesses, new causes are emerging as important contributors of childhood morbidity and mortality in India, e.g. congenital malformations, immunological disorders, accidents and mental health problems.

1.3 DETERMINANTS OF CHILD HEALTH

Child health in a community is influenced by various environmental factors, which account for geographic and demographic differences in morbidity and mortality.

TABLE 1.3: Leading causes of childhood morbidity and mortality in India

Prenatal/intranatal	*Neonatal*	*Post-neonatal*	*1–4 years*
Maternal nutrition Maternal illness/infections Obstetric complications Fetal malformations Fetal hypoxia	LBW and prematurity Birth asphyxia/injury Neonatal sepsis Congenital malformations	Acute respiratory infections Acute diarrheal diseases Malnutrition Congenital malformations	Acute respiratory infections Acute diarrheal diseases Malnutrition VPDs—TB, measles Accidents/poisoning
28 weeks ← PNR → 7 days		—	—
—	NMR	PNMR	—
—	← IMR →		—
—	← Under-five mortality rate →		

VPD: Vaccine preventable diseases; **LBW:** Low birth weight; **PNR:** Perinatal mortality rate; **NMR:** Neonatal mortality rate; **PNMR:** Post-neonatal mortality rate; **IMR:** Infant mortality rate.

Important adverse factors for child health in India include:

- *Maternal factors*, e.g. young maternal age, maternal malnutrition and illnesses, repeated pregnancies, short birth spacing, etc.
- *Socioeconomic factors*, e.g. poverty, urbanization, large family size, female illiteracy, girl child, illegitimate pregnancies, etc.
- *Cultural factors*, e.g. early marriage, improper infant feeding practices, e.g. top feeding, harmful child care customs/taboos, etc.
- *Environmental factors*, e.g. overcrowding, unsafe water supply and excreta disposal, poor personal and environmental hygiene, stressful family environment, e.g. broken families, etc.
- *Health care factors*, e.g. inadequate antenatal care, unsafe/untrained deliveries, poor immunization coverage, inadequate access to health services, etc., specially in rural areas.

Table 1.4 depicts status of some important health determinants in India, including perinatal care, early infant feeding, immunization and utilization of health care services in children.

1.4 INTERVENTIONAL STRATEGIES IN CHILD HEALTH

Globally, the needs and rights of children have been recognized since long with celebration of ***Universal children day*** on 14th November every year since 1954. Year 1979 was also celebrated as the ***UN international year of the child***.

Indian constitution has acknowledged the needs and rights of children under following articles:

- Article 24—prohibits employment of children <14 years in factories
- Article 39—prevents abuse of children of tender age
- Article 45—provides free and compulsory education until 14 years of age.

TABLE 1.4: Current status of child health determinants (NFHS-5, 2019-2021)

Antenatal care	
Adequate number (4) of ANC visits	58.1%
Iron-folic supplements for 100 days	44.1%
Tetanus immunization	92.0%
Perinatal care	
Institutional deliveries	88.6%
Unsafe deliveries	10.6%
LSCS deliveries	21.5%
% LBW or low birth weight	18.0%
Infant feeding practices	
Early breastfeeding (within <1 hour)	41.8%
Exclusive breastfeeding till 6 months	63.7%
Initiation of complementary feeds @ 6 months	45.9%
Adequate diet in breastfed (6–23 mo)	11.1%
Adequate diet in non-breastfed (6–23 mo)	12.7%
Immunization coverage	
Complete immunization till 23 months	76.4%
BCG	95.2%
DPT/Penta V (3 doses)	86.7%
OPV (3 doses)	80.5%
Measles 1 and 2	87.9%/31.9%
Rotavirus	36.4%
Vitamin A supplement in last 6 months	71.2%
Health care utilization	
% ARI cases visiting health care facility	69.0%
% Diarrhea visiting health care facility	68.9%
% use of ORS in diarrhea	60.6%
% use of zinc in diarrhea	30.5%

Source: NFHS-5 Fact sheet 2021 (reference 2019-21 data)

To fulfil these constitutional provisions, Government of India adopted a ***national policy for children (1974),*** which affirms that *"It shall be the policy of the state to provide adequate services to children, both before and after birth and through the period of growth, to ensure their full physical, mental and social development. The state shall progressively increase the scope of such services so that, within a reasonable time, all children in the country enjoy optimum conditions for their balanced growth."*

To achieve this objective, Government of India has proposed and revised some health targets to be achieved in a time-bound manner, aligned to global goals, e.g. millennium development goals (MDGs), sustainable development goals (SDGs) and WHO recommendations. *National health policy 2017* has established certain health goals to be achieved in time-bound manner, some of whom are related to child health as enlisted in **Table 1.5**.

Since independence, a plethora of targeted child health programs were launched in India with periodic reviews and modifications (Ch 28.4). While earlier programs were largely unisectorial, inter-sectorial coordination and integration with universal health care is hallmark of current strategies in child health strategies. Some important aspects of these efforts are as follows:

- **General population measures**
  - Socioeconomic development
  - Population control (family planning)
  - Safe water supply
  - Environmental sanitation
  - Promotion of female literacy
- **Reproductive female health measures**
  - Nutritional/health care of reproductive females
  - Adequate birth spacing
- **Antenatal care**
  - Regular antenatal care
  - *'At-risk approach'* for high-risk pregnancies
- **Perinatal care**
  - Safe/clean delivery by trained attendants
  - Essential newborn care
  - Promotion of breastfeeding
- **Postnatal care**
  - Universal immunization
  - Growth monitoring and promotion
  - Early diagnosis and treatment of common illnesses
  - Promotion of low-cost tools, e.g. ORS
- **Strengthening of health care system**
  - Low-cost medical care
  - General health programs, e.g. RCH, ICDS
  - Disease-targeted programs, e.g. NTEP, NVBDCP
  - Group-targeted programs, e.g. street children.

To conclude, child health in India is currently at the crossroads. Despite all efforts, status of Indian child is still far behind than that of a child in developed countries. Country has largely failed to achieve child health targets set time to time.

While lessons have been learnt from the past and strategies are being revised accordingly, achievement of these targets remains a function of political will, community participation, efforts of health workers and above all, acceptance of interventions by recipients.

TABLE 1.5 National Health Policy 2017: Targets with (proposed year of achievement)

Mortality indicators	
IMR	28 (2019)
Under-5 MR	23 (2025)
MMR	100 (2020)
NMR	16 (2025)
SBR	Single digit (2020)
Disease elimination/control	
HIV	90:90:90* (2020)
Malaria (annual incidence)	<1: 1000 (2020)
Leprosy elimination	<1: 10000 (2018)
Kala-azar elimination	<1: 10000 (2017)
Lymphatic filariasis elimination	2017**
TB cure rate/elimination	85% (2025)
Health services	
Antenatal coverage	90% (2025)
Full immunization till 1 yr	90% (2025)
Stunting (under-5 children)	Reduce by 40% (2025)
Safe water and sanitation	100% by 2020

*90% PLHA know their HIV status, 90% receive sustained antiretroviral therapy and 90% on antiretroviral therapy will have viral suppression.
**<1% microfilaria prevalence in all districts.

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CHAPTER

2

Normal Growth and Development

Surbhi Rathi, Priyanka Bote, Mukesh Agrawal

Growth and development is the essence of childhood that leads to transition of a fertilized ovum into an independent adult through different stages of anatomical growth and physiological maturation. While the terms *growth* and *development* are not interchangeable, both processes are largely interdependent.

Growth is *an anatomical process involving increase in the physical size of an organ, tissue and body, by multiplication or enlargement of cells*. It can be easily measured in terms of increase in anthropometric parameters.

Development denotes *physiological or functional maturation of various organs or systems, acquisition of newer functions or skills and adaptation to the environment*. Unlike growth, precise measurement of development is difficult, though the achievement of various neurological milestones may be used as general indicator of development.

2.1 DETERMINANTS OF GROWTH AND DEVELOPMENT

Growth and development is a complex process that depends on the inherent biological potential as well as various environmental influences including social, emotional and pathological factors **(Table 2.1)**. Important factors affecting growth and development in children are as follows:

I. Intrinsic (biological) factors determine the inherent pace, pattern and ultimate potential for growth and development, achievable under best environmental situations and include:

- ***Age:*** General pace of growth is highest in intrauterine life and early infancy, decelerates gradually with advancing childhood, followed by a second growth-spurt with onset of puberty.
- ***Sex:*** Boys are usually heavier and taller than girls in early childhood but puberty begins and completes earlier in girls.
- ***Ethnicity*:** Caucasians and children of developed countries have better growth, not only due to inherent potential but also due to favorable environmental factors, e.g. good nutrition and lesser infections.

TABLE 2.1: Factors affecting growth and development

I. Intrinsic (biological) factors
- Age, sex and ethnicity
- Hereditary trends
- Genetic/chromosomal disorders

II. Extrinsic (organic) factors
- *Prenatal*
  - *Maternal nutrition:* Malnutrition and anemia
  - Intrauterine (TORCH) infections*
  - *Maternal diseases:* Hypertension and diabetes
  - *Teratogens:* Drugs, radiation, smoking
  - Placental disorders/insufficiency
- *Perinatal*
  - Gestational age and birth weight
  - *Complications:* Birth asphyxia and kernicterus
- *Postnatal*
  - *Nutrition:* Malnutrition and anemia
  - *Chronic infections:* TB, worm infestations
  - *Systemic illnesses:* CHDs and asthma
  - *Trauma:* Head injury
  - *Drugs:* Steroids and cytotoxic agents

III. Extrinsic (environmental) factors
- Socioeconomic factors
- Cultural factors/practices
- Emotional stimulation
- Climatic factors

*TORCH: Toxoplasmosis, rubella, cytomegalovirus, herpes simplex.

- ***Hereditary:*** Children of taller parents are usually tall and *vice versa*. Age of menarche in daughters usually correlates well with that in their mothers.
- ***Genetic disorders*** are associated with inherently altered growth potential, e.g. short stature in Turner syndrome, Achondroplasia, etc. and tall stature in Marfan syndrome, etc.
- ***Secular trends*** suggests very small but consistent rise in normal weight/height values of the children at different ages over the decades, perhaps due to better environmental factors, e.g. nutrition and freedom from infections. Similar trends are noticed in terms of better final adult height and earlier age of menarche in girls. These secular trends are more marked in developing

countries due to the scope for improvement and underline the need for periodic revision of reference values.

II. Extrinsic (organic) factors are prime determinants of growth and development in developing countries, which directly facilitate or limit the achievement of inherent growth potential. The exact effect of these factors depends on the age, quantum and duration of exposure in relation to the period of growth. Important organic factors affecting growth/development include:

- ***Prenatal factors*** involving maternal health, e.g. malnutrition, infections and systemic diseases affects growth of offsprings in three different ways: (a) during the period of organ differentiation, i.e. *embryogenesis*, leading to higher risk of abortions or congenital malformations, (b) during late fetal phase of anatomical and functional maturation, leading to intrauterine growth retardation (IUGR) or stillbirths, (c) during postnatal life, when maternal ill-health may affect emotional attention and quality of baby care during critical phase of growth.
- ***Obstetrical or perinatal factors:*** Preterms and IUGR babies behave differently than term babies during postnatal growth period—while preterms grow faster in late infancy (*catch up growth)* than the term babies, IUGR babies are unlikely to show significant catch-up growth and have limited growth potential throughout the life. Other perinatal events, e.g. asphyxia, injuries, sepsis, kernicterus, etc. may also have disastrous effects on subsequent growth and development.
- ***Postnatal factors:*** Postnatal growth is largely governed by hormonal influences, e.g. growth hormone in pre-pubertal period and sex-steroids during puberty; apart from adequate supply of substrates, e.g. nutrition, oxygen, etc. and freedom from infections. Malnutrition, chronic infections, e.g. tuberculosis and systemic illnesses, e.g. asthma, heart diseases, etc. are important adverse factors influencing postnatal growth and development. Head injury may lead to intellectual disability while growth of a particular limb may be affected after fractures of long bones. Prolonged steroid/cytotoxic therapy are important causes of iatrogenic growth suppression.

III. Extrinsic (environmental) factors are important hindrances for normal growth in developing countries, which indirectly affect nutrition, infection rate and quantum of health care. These include:

- ***Socioeconomic factors:*** Children of affluent parents have better growth due to better nutrition and hygienic conditions than those of low socio-economic status.
- ***Cultural factors*****:** Child-rearing practices vary indifferent communities, which may significantly impact child's growth. Routine practice of breast-feeding is a positive growth-promoting factor, while delayed weaning, food taboos and unhygienic living conditions are important adverse cultural influences in India.
- ***Emotional factors:*** Adequate emotional stimulation is essential not only for psychosocial and linguistic development of a child but also for growth. Lower growth hormone levels are well documented in emotionally deprived children like orphans.
- ***Climatic factors:*** Growth is slower in summer than in spring season, probably as infections are common and appetite is poor in hot and humid climate. Climate also affects the food productivity.

2.2 LAWS AND PATTERNS OF GROWTH

Although each child has a unique pace of growth, certain principles are applicable to all children, as follows:

- **Growth is a continuous and orderly process** that begins with fertilization of ovum and continues at *every moment* of intrauterine and postnatal life till puberty, in a fairly consistent order.
- **Pace of growth in not uniform throughout childhood**, with intermittent periods of rapid growth, also termed as *critical periods*. Various *phases or periods of growth* **(Table 1.1)** may be broadly classified as follows:
  - ***Embryonic period*** (0–8 weeks) is the period of explosive growth in the number of cells following fertilization and implantation of the ovum in uterus as well as organ differentiation, i.e. formation of various tissues and organs. Any insult in first trimester is more likely to cause congenital malformations. By the end of this period, a fetus is structurally similar to an adult, except the differences in organ size and function.
  - ***Fetal growth*** (9^{th} week to birth) is characterized by increase in size of organs (anatomical development) and functional maturation of various systems (physiological development). Intrauterine fetal growth follows an S-shaped curve with maximum growth in terms of weight gain during 24–37 weeks of life (15 gm/day) followed by gradual decline to ~6 gm/day between 37–40 weeks. However, growth in fetal length peaks at ~20 weeks with a gain of ~1 cm/month followed by gradual slow-down.

    Any insult in late pregnancy leads to restrictions in body size and organs, termed intrauterine growth retardation or IUGR. While a fetus is usually capable to survive *ex-utero* beyond 28^{th} weeks of life (*age of viability*), adequate functional maturation is achieved only by 37 weeks (*full term*).
  - ***Postnatal growth*** during childhood (birth to onset of puberty) involves further physiological maturation and anatomical growth, though the pattern and pace of these changes differ in different

body tissues and in different individuals, discussed later (see next law below).

– ***Adolescent growth and development*** from onset to completion of puberty, is the transitional phase between child and adult, characterized by (a) *physical growth* spurt to attain adult dimensions, (b) *sexual maturity*, and (c) *psychological changes* in order to gain emotional and functional independence (Ch 13.3). Girls have an earlier onset of physical growth spurt during adolescence (9–12 years) than boys (12–15 years).

- **Pattern of growth is different in different body tissues.** All tissues or organs do not grow at the same velocity at same age. Mainly four types of growth patterns are seen in different body tissues **(Fig. 2.1)**.
  – ***Somatic growth*** is maximum in intrauterine life and follows a sigma-shaped curve in postnatal life, with two distinct growth spurts - during infancy and during adolescence. In mid-childhood, child grows slowly but steadily. Somatic growth completes at 16–18 years (earlier in females) with achievement of adult height.
  – ***Neurological growth*** is maximum in late intrauterine and early postnatal life, followed by rapid deceleration in late infancy and is nearly complete by two years of age. Head circumference reaches to ~95% of adult value by 2–3 years of age and any further increase is due to the increase in bony thickness rather than the brain size.
  – ***Gonadal growth*** is negligible till the onset of puberty, when gonads grow rapidly under endocrinal influences to achieve adult size and function during next 3–4 years of adolescence.
  – ***Lymphoid growth*** is maximum in mid-childhood, during 4–8 years of age. Thus, lymph nodes, tonsils and adenoids are physiologically enlarged in this age group, often confused with a diseased state. Subsequently, these tissues partially regress to adult size after 8–9 years of age.
- **Pace of growth is unique for every child**, despite comparable growth potential, determined by familial and racial characteristics. Each child experiences intermittent periods of growth spurts and stagnation. While some children grow rapidly in early life followed by slower pace, others have initially slower growth followed by late catch-up growth.
- **Growth progresses in cephalocaudal direction:** During intrauterine life, head and upper torso grows faster than limbs as evident from higher upper *vs* lower segment (US:LS) ratio at birth (1.7:1) and the head being larger than the chest. Postnatally, trunk and limbs grow more rapidly with equalization of Head : Chest circumference at 1 year and US:LS ratio at 7 years. Chest circumference exceeds head circumference beyond first year of life.

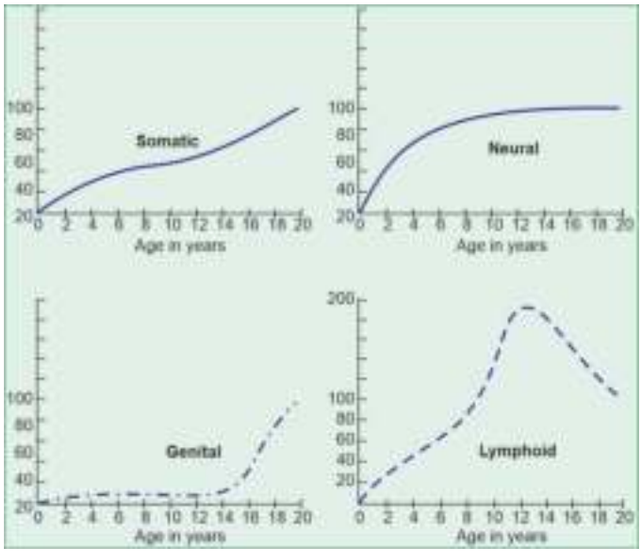

Fig. 2.1: **Growth patterns in different body tissues.**

2.3 NORMAL CHILDHOOD GROWTH

Physical growth during childhood is evident in many dimensions by chronological changes in body size and appearance, i.e. anthropometric indicators **(Table 2.2)** as well as in others tissues, e.g. dentition, skeletal maturation, and internal body composition. Despite individual variations, most of these changes follow a predictable pattern and any significant deviation from this pattern may be the earliest or only indicator of ill health.

TABLE 2.2: Anthropometric indicators

I. Anthropometric

Primary
- Weight[1]
- Length or height[1]
- Head circumference[1]
- Chest circumference[1]
- Mid-arm circumference[1]
- Arm span[3]
- Sitting Height[3]
- Skin-fold thickness[2]

Derived
- Weight for height[2]
- US: LS ratio (CR:RH ratio)[3]
- Stem stature index[3]
- Body mass index (BMI) [2]

II. Clinical
- Body build
- Dentition
- Sexual maturity rating (SMR)

III. Radiological:
- Bone age

Should be recorded in: [1]in all children, [2]in malnourished/obese children, [3]in short/tall stature

US: Upper segment; **LS:** Lower segment; **CR:** Crown to rump; **RH:** Rump to heel.

This chapter deals with some important patterns of growth during childhood, while adolescent growth and sexual maturity has been discussed in later chapter 13.2.

2.3.1 SOMATIC (ANTHROPOMETRIC) GROWTH

Change in the body size and appearance is most obvious dimension of growth, which can be easily measured by various anthropometric parameters as follows:

Weight is the most sensitive indicator of physical growth, used not only for regular monitoring but also for early detection of diseases/recovery and calculation of drug dosages. While precise values of body weight in normal children depend on the sex, race and other factors, as reflected in growth norms/charts discussed later, a general pattern is as follows:

A normal baby weighs ~3.3 kg at birth and looses ~10% of birth weight during first 7 days of life, which is regained by 10th day. Subsequently, they gain ~20–30 gm/day during first 3 months, ~400 gm/month during 3–12 month, ~2 kg/year till 7 years and then, ~3 kg/year subsequently till end of puberty.

Birth weight usually doubles at five months (~6.5 kg), triples at one year (~10 kg), quadruples at two years (~12 kg) and becomes seven times by 7 years (~21 kg) of age. A simple method to calculate normal Wt at different ages is given in **Table 2.3** (for precise values, *see* **Table 2.6A and B)**.

Stature, i.e. cephalocaudal distance is measured in terms of recumbent ***length*** up to two years of age and *standing* ***height*** in older children. Stature is an indicator of long-term growth, affected only after prolonged growth insult for many months. While precise values of stature in normal children depend on the sex, race and other factors, as reflected in growth norms/charts discussed later, a general idea is as follows:

At birth, a term newborn measures ~50 cm. Subsequently, the length increases by ~4 cm/month till 3 months (~62 cm at 3 months), then ~2 cm/month till 6 months (~69 cm at 6 months) and then ~1 cm/month till one year (~75 cm at one year).

A child gains about half of the birth length, i.e. ~25 cm in first year of life (~75 cm), half of the first-year gains, i.e. ~12.5 cm in second year (~ 87.5 cm), half of the second year gains, i.e. ~6.5 cm in third year (~94 cm) and then ~5–6 cm/year till the onset of puberty. A simple method to calculate normal length/height at different ages is given in **Table 2.4** (For precise values, *see* **Table 2.6A and B)**.

Parental height is an important determinant of children's height. Height of a boy at 2 years and girls at 2.5 years is nearly half of the adult height (+ 5 cm). It is possible to predict the adult height in children from parental heights, using the following formulas:

Adult Ht* (boy) = {(Mother's Ht +13) + Father's Ht}/2
Adult Ht* (girl) = {(Father's Ht – 13) + Mother's Ht}/2
(predicted adult Ht + 8 cm)*

Head circumference is the indirect indicator of brain growth and must be measured in all children up to 5 years of age. Brain growth is nearly complete by then and any further increase in head circumference of older children is minor and due to thickening of calvarium rather than changes in brain size. While precise values of head circumference in normal children depend on the sex, race and other factors, as reflected in growth norms/charts discussed later, a general idea is as follows:

At birth, normal head circumference is ~33 cm, increases by ~2 cm/month till 3 months (~39 cm at 3 months), ~1.5 cm/month in next 3 months (~43 cm at 6 months) and ~0.5 cm/month in next 6 months (~47 cm at 1 year). Subsequently, it increases by only ~2 cm in second year (~49 cm at 2 years), ~1 cm in third year (~50 cm at 3 years) and <1 cm/year afterwards. For precise values of head circumference up to 5 years, *see* **Table 2.6A and B**.

Dine's formula may be used in first 400 days of life to express relationship between length and head circumference with accuracy of ~95%, as follows:

Head circumference ± 2.5 = Length/2 + 9.5
(all values in cm)

Smaller head size (<3rd percentile) indicates microcephaly or craniosynostosis, while larger head (> 97th percentile) is seen in hydrocephalus, macrocephaly, rickets, or chondrodystrophies.

Mid-upper arm circumference (MUAC) is a measure of circumferential growth of soft tissue including fat and muscles. After rapid growth in first 6 months of life,

TABLE 2.3: Simplified weight calculations

Birth weight (BW)	:	3.3 kg
0–4 months	:	BW + (age in months × 0.8)
4–8 months	:	BW + (age in months × 0.7)
8–12 months	:	BW + (age in months × 0.6)
1–9 years	:	(Age in years + 4) × 2
9–12 years	:	Age in years × 3

TABLE 2.4: Simplified length/height calculations

At birth	50 cm
Gains in first year	
0–3 months	4 cm/month
3–6 months	2 cm/month
6–12 months	1 cm/month
At 1 year	75 cm
At 2 years	87.5 cm
At 3–12 years	(Age in years × 6) + 77*

*Weech's formula

MUAC remains largely constant (~16–17 cm) between 2–5 years of age, due to replacement of body fat with muscle mass.

A MUAC <13.5 cm between 1–5 years of age indicates acute malnutrition, forming the basis of its diagnosis and classification (severe <11.5 cm,/moderate 11.5–12.4 cm).

Chest circumference is ~3 cm less than the head circumference at birth, equals at one year and exceeds afterwards. It needs to be measured only in children <2 years at nipple level during mid-expiration by encircling the non-stretchable measuring tape perpendicular to chest using cross-over technique.

Persistence of chest circumference less than head circumference beyond infancy indicates larger head, e.g. hydrocephalus or smaller chest, e.g. malnutrition.

Body proportions, i.e. ratio between torso and limbs may be altered in some disorders with short/tall stature. Various terms are used to denote these proportions, e.g. upper-segment *vs* lower-segment ratio (*US:LS ratio*), crown-to-rump *vs* rump-to-heel ratio (*CR:RH ratio*) and *stem-stature index* (sitting Ht/standing height × 100).

To calculate these ratio/index, measure lower-segment height in standing position from pubic symphysis to the floor and deduct it from total standing height to derive upper-segment height.

At birth, upper segment is longer than the lower-segment. Postnatally, lower-segment grows more rapidly to equalize upper segment by 7–10 years. Thus,

- *Normal US: LS ratio* is ~ 1.7:1 at birth, 1.3:1 at three years and 1:1 at seven years onwards.
- *Normal stem-stature index* is ~70 at birth, 66 at six months, 64 at one year, 61 at two years, 58 at three years, 55 at 5 years, and 52 at 7 years.

US:LS ratio is *increased* in short-limb dwarfism, e.g. achondroplasia, cretinism and severe rickets; and decreased or reversed in short-trunk dwarfism, e.g. spondyloepiphyseal dysplasia, spinal deformities and Marfan syndrome.

Limb span, i.e. the distance between tips of middle fingers of outstretched hands, is another measure of body proportions, being normally 1–2 cm less than the height till 10 years of age and equals or more afterwards. Disproportionate increase or decrease in limb span as compared to height indicates short-trunk or short-limb dwarfism respectively.

Skin-fold thickness is an indicator of body fat and must be measured in selected children over the left triceps area by a *Lange* or *Harpenden's* skin-fold calipers. A skin-fold thickness of <10 mm after infancy indicates malnutrition (<6 mm in severe malnutrition).

Body mass index (BMI) is an indicator of subcutaneous fat, calculated as weight in kg/Ht in m^2. Normal BMI ranges between ~18.5–23 kg/m^2 after first 5 years of life.

Rather than growth assessment, BMI is more useful for the diagnosis of obesity or overweight in children >2 years and undernutrition in children >5 years of age. Nutritional status may be classified on the basis of BMI as follows: obesity (>27), overweight (>23), normal (18.5–22.9), thinness (<18.5) and moderate/severe thinness (<17). For precise values, *see appendix 2.11–2.12.*

Body Build (Somatotypes)

Body build (somatotype) refers to visual physical appearance of normal children (excluding craniofacial features), which is often determined by hereditary and racial characteristics. Three main types of normal body build or somatotypes, as per *Sheldon's classification* are:

a. ***Ectomorphic:*** Tall and linear build, with small musculature and lighter bone structure.

b. ***Endomorphic:*** Stocky-rounded build, with large amount of soft tissue.

c. ***Mesomorphs:*** Heavy muscular physique, between the ectomorphs and endomorphs.

2.3.2 DENTAL DEVELOPMENT (DENTITION)

Dental development may be divided into 3 chronological stages—(a) eruption of primary or deciduous teeth, (b) exfoliation of these teeth, and (c) eruption of permanent teeth **(Table 2.5)**, though the timings of these events are too variable to be useful for growth assessment.

Normal dentition: Important events in normal dentition include:

- Total numbers of deciduous and permanent teeth are 20 and 32 respectively. *There are no deciduous premolars and third molars.*
- Primary dentition begins at 5–8 months with eruption of *lower central incisor* (first deciduous teeth) and completes by 2–2.5 years with eruption of second molars. A baby has ~6 primary teeth at one year and ~12–16 teeth at 2 years.
- Exfoliation of deciduous teeth begins at ~6 years, usually with loss of *first molar*. Delayed shedding of deciduous teeth may lead to dental mal-alignment.

TABLE 2.5: Chronology of dentition

Deciduous teeth		*Permanent teeth*	
Age (months)	***Erupting teeth***	***Age (years)***	***Erupting teeth***
5–8	Central incisors	6–7	First molars
7–11	Lateral incisors	6–8	Central incisors
10–16	First molars	7–9	Lateral incisors
16–20	Canines	9–12	Canines
20–30	Second molars	10–12	First premolars
–	–	10–13	Second premolars
–	–	12–13	Second molars
–	–	17–23	Third molars

- Permanent dentition begins ~2–4 months after exfoliation of first deciduous tooth (usually first molar) and continues well beyond the childhood till eruption of third molars (*wisdom teeth*) at 17–23 years.

Abnormal dentition: Common developmental abnormalities in dentition include:

Natal teeth are occasionally present at birth as supernumerary or prematurely erupted deciduous teeth. These teeth are usually harmless and should be extracted only if loose or interfere with feeding.

Delayed dentition, i.e. no primary tooth till 12 months of age, may be due to: (a) familial tendency, (b) nutritional deficiency, e.g. PEM or rickets, (c) local gingival disease, e.g. gum fibrosis, (d) inherited defects of dentin, e.g. osteogenesis imperfecta, and (e) endocrinal disorders, e.g. hypothyroidism or hypoparathyroidism.

Anodontia, i.e. absolute non-eruption of teeth, is seen in ectodermal dysplasia.

Discolored teeth usually indicate tetracycline therapy in early childhood (yellow staining), malnutrition, prolonged illness (discrete pit lines) or poor oral hygiene.

Premature exfoliation of tooth is common in dental caries, trauma and gingivitis. Rarely, recurrent tooth loss may also indicate histiocytosis or cyclic neutropenia.

2.3.3 SKELETAL MATURATION

Skeletal maturation begins *in utero* with formation of endochondral bones, followed by appearance of ossification centers and completion of ossification, which continue in postnatal life.

Normal maturation: It is important to note that:

- Earliest epiphyseal centers to appear are for *os calcis* and *talus*, at 22–26 weeks of intrauterine life.
- *At birth*, a term newborn has total *five* ossification centers for distal end of femur, proximal end of tibia, head of humerus, calcaneus and talus.
- Clavicle, mandible and membranous bones of skull are already ossified at birth.
- Skeletal maturation is faster in girls than in boys.
- Ossification centers appear earlier on left side of body.

Appearance, maturation and fusion of various epiphyseal centers for ossification is commonly used as the determinant of skeletal maturation or bone age.

Indications for bone age determination are – (a) evaluation of short stature; (b) prediction of adult height in cases with early/late onset of puberty, and (c) medico-legal purposes.

Assessment of bone age requires the knowledge of normal skeletal maturation, its variability and selection of proper X-ray (conventionally of left side) for assessment, as follows:

- *Bone age in newborn* is assessed by knee X-ray, to see the presence of epiphyseal centers for lower end of femur and upper end of tibia. Absence of these centers at birth usually indicates *prematurity* or *hypothyroidism.*
- *Bone age in infancy* is difficult to determine due to extreme variability in early skeletal maturation.
- Postnatally, first ossification centers appear for: (a) two carpal bones, i.e. capitate and hammate at ~6 months, and (b) upper end of humerus at ~ 5 months of age. X-ray of left wrist joint and shoulder is preferred to determine bone age in late infancy.
- *Bone age beyond infancy* may be assessed by number of carpal ossification centers in X-ray of left wrist, i.e. *Bone age = Number of centers – 1.* Thus, a six years old child has ~7 carpal centers, while the last or eight carpal center (for pisiform) appears only at 12–13 years.
- *Bone age in early adolescence* is determined by X-ray of left elbow to see the centers for distal end of ulna and lesser trochanter, which appear at ~ 12 years of age. Fusion of capitulum with the shaft at elbow predicts onset of puberty within one year.
- *Bone age in late adolescence* is assessed on X-ray of left hip to see the center for iliac crest, which appears at ~ 16 years.

Commonly, *Greulich-Pyle atlas* or *Tanner-Whitehouse-2 individual bone method* is used for assessment of bone age.

Common abnormalities in skeletal maturation include:

- ***Delayed bone age in:*** (a) prematurity (physiological), (b) nutritional deficiency, e.g. severe malnutrition, rickets, (c) endocrinal disorders, e.g. hypothyroidism, hypopituitarism, and (d) genetic disorders, e.g. Down syndrome, epiphyseal dysplasias, etc.
- ***Advanced bone age*** in endocrinal disorders, e.g. thyrotoxicosis, adrenal hyperplasia, precocious puberty, gigantism, pseudohypothyroidism. Bone age may be advanced *only in affected bones* in rheumatoid arthritis and arteriovenous malformations.

2.3.4 BODY COMPOSITION

Although of little importance in assessment of growth, it is noteworthy to remember following changes in body composition with age:

- *Decrease in total body wate*r from ~75% at birth to ~60% in adults, as well as its redistribution with gradual decrease in extracellular water and increase in intracellular water.
- *Increase in skeletal muscle mass*, from ~25% at birth to ~45% in adults.
- *Changes in adipose tissue mass*, which is higher in infancy and adolescence, i.e. ~25%, as compared to mid-childhood, i.e. ~20%.
- *Changes in chemical composition* of lean body mass, due to accumulation of various minerals.
- *Changes in visceral size*, which usually follow the changes in body size with some exceptions, e.g. postnatal regression of thymus.

2.4 GROWTH NORMS AND GROWTH CHARTS

Normal or reference values for common growth parameters in healthy children are obtained by longitudinal or cross-sectional surveys of the selected population with an appropriate sample size. However considering individual variations even in healthy population, data obtained during these surveys is further analyzed by various statistical methods to disregard normal variations, in terms of medians, percentiles and Z-scores.

Medians, Percentiles and Z-scores: When a parameter, e.g. weight of the large number of children is recorded in a given population with comparable age and sex, values are expected to differ from each other but all variations are not abnormal. When this data is arranged in an ascending or descending order, it is expected to form a bell-shaped curve (Gaussian distribution) with maximum values clustered around the center of this curve and fewer values at both ends.

Median value: *If the data, (e.g. weight/height) from a sample population of 100 children is arranged in ascending or descending order, the weight/height of the 50th child is likely to be essentially normal and reflects the median value.* On the other hand, children at the extremes of this arrangement are more likely to be abnormal.

Percentiles *mean the location of a child's value in above arrangement.* For example, the anthropometric value of 3rd, 25th, 50th, 75th or 97th child in this series is designated as 3rd, 25th, 75th and 97th percentile respectively. Values between 3rd and 97th percentile cover 95% of children and correspond with 2 standard deviations (SD) of mean value on Gaussian distribution—a universally acceptable limit for variations. For information, one SD covers 68% of values (16th-84th percentile) and three SD covers 97% of values in this data series (2nd-98th percentile).

In practice, 50th percentile is considered as ideal value, 3rd percentile as the lowest acceptable limit of normal value and 97th percentile as highest acceptable normal value. Thus, children with weight, height or other parameters below the 3rd percentile or above the 97th percentile are considered as potentially abnormal, while those within these limits are considered as potentially normal.

Z-score is another common term used to denote *deviation of observed value from the median value* and calculated as follows–

Observed value - Median value/standard deviation.

A Z-score of 2 means that the difference between observed value and expected reference value is 2 times of standard deviation in reference population, with prefix +/- sign (+1,+2,+3 Z-score or -1,-2,-3, Z-score) denoting the observed value being more or less than the reference values. A Z-score between +2 and -2 covers 95.4% of observations and is generally considered as limits of normalcy.

Growth norms and Growth charts: Results of these surveys, after statistical analysis, are depicted eiher in numerical tabular form *(Growth norms)* or visual graphic form *(Growth charts)*. Thus, growth norms or charts reflect normal anthropometric values in healthy children of different ages and gender, within the acceptable limits of individual variations.

Standard vs Reference norms: While the term *standard norms* and *reference norms* for growth are often used interchangeably, two terms have different connotations.

- *Reference norms for growth* are derived from the local population with similar environmental, socioeconomic and nutritional characteristics and represent that - *'how does the concerned population grow ?'.*
- *Standard norms for growth,* on the other hand, are derived from the much healthy population, relatively free from common constraints, e.g. malnutrition of infections. And denote that '*How should the child grow?',* If not constrained by other factors.

WHO vs IAP Growth norms: WHO, in 2006, published Standard growth norms for children below 5 years, derived from a multicenteric study of six countries in different regions of the world – Brazil, India, Ghana, Norway, Oman and United States. Study included populations with healthy practices, e.g. breastfeeding and no maternal smoking during pregnancy.

WHO standard growth norms are available for many anthropometric parameters including those for weight, length/height, weight for height, head circumference and body mass index in the tabular as well as graphic forms ***(Appendix 2.1–2.8)***. Government of India has adopted WHO growth standards for use in children <5 years. These standards are aspirational models, which define *how the under-five children of the world should grow*, rather than *how they actually grow ?*

For older children, WHO suggests use of country-specific growth standards, as growth in this age-group is often influenced by local environmental factors and timing of the puberty.

Indian Academy of Pediatrics (IAP) in 2015, published reference growth norms for Indian children between 5–18 years, for many anthropometric parameters, e.g. weight, height, and body mass index; in tabular as well as graphic forms ***(Appendix 2.9–2.12)***. Recently in 2021, IAP has also published WHO and IAP charts in combination for use in children from birth to 18 years.

Tables 2.6A and B provide abridged versions in tabular form of WHO norms for children < 5 years and IAP norms for those aged 5–18 years, for selected anthropometric parameters for quick reference.

TABLE 2.6A: WHO child growth standards for weight (kg), height (cm) and head circumference (cm)

Boys							Girls					
Weight		Height		Head		Age	Weight		Height		Head	
3.3	(2.5–4.3)	**49.9**	(46.3–53.4)	**34.5**	(32.1–36.9)	**Birth**	**3.2**	(2.4–4.2)	**49.1**	(45.6–52.7)	**33.9**	(31.7–36.1)
6.4	(5.1–7.9)	**61.4**	(57.6–65.3)	**40.5**	(38.3–42.7)	**3 m**	**5.8**	(4.6–7.4)	**69.8**	(55.8–63.8)	**39.5**	(37.2–41.9)
7.9	(6.4–9.7)	**67.6**	(63.6–71.6)	**43.3**	(41.0–45.6)	**6 m**	**7.3**	(5.0–9.2)	**65.7**	(61.5–70.0)	**42.2**	(39.7–44.6)
8.9	(7.2–10.9)	**72.0**	(67.7–76.2)	**45.0**	(42.6–47.4)	**9 m**	**8.2**	(6.6–10.4)	**70.1**	(65.6–74.7)	**43.8**	(41.3–46.3)
9.6	(7.8–11.8)	**75.7**	(71.3–80.2)	**46.1**	(43.6–48.5)	**1.0 y**	**8.9**	(7.1–11.3)	**74.0**	(69.2–78.9)	**44.9**	(42.3–47.5)
10.9	(8.9–13.5)	**82.3**	(77.2–87.3)	**47.4**	(44.9–49.9)	**1.5 y**	**10.2**	(8.2–13.0)	**80.7**	(75.2–86.2)	**46.2**	(43.6–48.8)
12.2	(9.8–15.1)	**87.8**	(82.1–93.5)	**48.3**	(45.7–50.8)	**2.0 y**	**11.5**	(9.2–14.6)	**86.4**	(80.3–92.5)	**47.2**	(44.6–49.8)
13.3	(10.7–16.6)	**91.9**	(85.5–98.3)	**48.9**	(46.3–51.6)	**2.5 y**	**12.7**	(10.1–16.2)	**90.7**	(84.0–97.3)	**47.9**	(45.3–50.6)
14.3	(11.4–18.0)	**96.1**	(89.1–103.1)	**49.5**	(46.8–52.1)	**3.0 y**	**13.9**	(11.0–17.8)	**95.1**	(87.9–102.2)	**48.5**	(45.9–51.2)
15.3	(12.2–19.4)	**99.9**	(92.4–107.3)	**49.9**	(47.2–52.6)	**3.5 y**	**15.0**	(11.8–19.5)	**99.0**	(91.4–106.7)	**49.0**	(46.3–51.6)
16.3	(12.9–20.9)	**103.3**	(93.6–111.2)	**50.2**	(47.5–53.0)	**4.0 y**	**16.1**	(12.5–21.1)	**102.7**	(94.6–110.8)	**49.3**	(46.7–52.0)
17.3	(13.6–22.3)	**106.7**	(98.4–115.0)	**50.5**	(47.7–53.3)	**4.5 y**	**17.2**	(13.2–22.8)	**106.2**	(97.6–114.7)	**49.6**	(47.0–52.3)
18.3	(14.3–23.8)	**110.0**	(101.2–118.7)	**50.7**	(47.9–53.5)	**5.0 y**	**18.2**	(14.0–24.0)	**109.4**	(100.5–118.4)	**99.9**	(47.2–52.6)

Figures in bold denote 50th percentile while figures in parentheses denote lowest (3rd percentile) and highest (97th percentile) for respective age and sex.

Source: Modified from: WHO child growth standards 2006.

TABLE 2.6B: IAP growth reference norms 2014 for weight and height for Indian children 5–18 years

Boys					Girls			
Weight		Height		Age	Weight		Height	
17.1	(13.2–24.2)	**108.9**	(99.0–119.4)	**5.0**	**16.4**	(12.3–25.0)	**107.5**	(97.2–119.3)
18.2	(13.8–26.1)	**111.9**	(101.6–122.7)	**5.5**	**17.6**	(13.0–27.0)	**110.5**	(99.8–122.5)
19.3	(14.5–28.3)	**114.8**	(104.2–126.0)	**6.0**	**18.7**	(13.7–29.1)	**113.5**	(102.3–125.6)
20.7	(15.3–30.8)	**117.8**	(106.8–129.3)	**6.5**	**19.9**	(14.4–31.2)	**116.5**	(104.9–128.7)
21.9	(16.0–33.4)	**120.7**	(109.3–132.6)	**7.0**	**21.2**	(15.1–33.4)	**119.4**	(107.4–131.9)
23.3	(16.7–36.2)	**123.5**	(111.8–135.9)	**7.5**	**22.5**	(15.9–35.7)	**122.4**	(110.0–135.0)
24.8	(17.5–39.4)	**126.4**	(114.3–139.1)	**8.0**	**24.0**	(16.7–38.1)	**125.4**	(112.6–138.1)
26.4	(18.3–42.6)	**129.1**	(116.7–142.2)	**8.5**	**25.5**	(17.5–40.7)	**128.4**	(115.2–141.3)
27.9	(19.1–45.5)	**131.8**	(119.0–145.3)	**9.0**	**27.2**	(18.5–43.4)	**131.4**	(117.8–144.5)
29.4	(19.9–48.6)	**134.5**	(121.3–148.3)	**9.5**	**29.0**	(19.5–46.3)	**134.4**	(120.5–147.6)
31.1	(20.7–51.8)	**137.2**	(123.6–151.4)	**10.0**	**31.0**	(20.7–49.4)	**137.4**	(123.3–150.8)
32.8	(21.6–55.2)	**139.9**	(125.9–154.4)	**10.5**	**33.2**	(22.0–52.6)	**140.4**	(126.1–153.9)
34.7	(22.6–58.7)	**142.7**	(128.2–157.5)	**11.0**	**35.4**	(23.3–55.9)	**143.3**	(128.8–156.8)
36.9	(23.8–62.5)	**145.5**	(130.7–160.6)	**11.5**	**37.6**	(24.8–59.1)	**145.9**	(131.5–159.6)
39.0	(24.9–66.1)	**148.4**	(133.2–163.7)	**12.0**	**39.8**	(26.2–62.1)	**148.4**	(134.0–162.0)
41.2	(26.1–69.5)	**151.4**	(135.7–166.8)	**12.5**	**41.8**	(27.6–64.8)	150.5	(136.3–164.1)
43.3	(27.5–72.6)	**154.3**	(138.3–169.9)	**13.0**	**43.6**	(28.9–67.1)	**152.2**	(138.2–165.9)
45.7	(29.0–75.6)	**157.2**	(140.9–172.7)	**13.5**	**45.1**	(30.2–69.0)	**153.6**	(139.9–167.2)
48.2	(30.7–78.3)	159.9	(143.4–175.4)	**14.0**	**46.4**	(31.3–70.4)	**154.7**	(141.3–168.8)
50.8	(32.6–80.9)	**162.3**	(145.8–177.7)	**14.5**	**47.5**	(32.3–71.4)	**155.5**	(142.4–169.0)
53.1	(34.5–83.1)	**164.5**	(148.0–179.7)	**15.0**	**48.4**	(33.1–72.1)	**156.1**	(143.3–169.5)
55.2	(36.1–84.7)	**166.5**	(150.0–181.4)	**15.5**	**49.1**	(34.0–72.5)	**156.6**	(144.1–169.8)
56.8	(37.5–85.8)	**168.1**	(151.8–182.7)	**16.0**	**49.7**	(34.7–72.8)	**156.9**	(144.7–170.1)
58.2	(38.7–86.8)	**169.6**	(153.4–183.8)	**16.5**	**50.3**	(35.5–73.1)	**157.2**	(145.2–170.2)
59.5	(39.8–87.5)	**171.0**	(155.0–184.8)	**17.0**	**50.9**	(36.2–73.3)	**157.4**	(145.7–170.4)
60.6	(40.8–88.0)	**172.3**	(156.6–185.8)	**17.5**	**51.5**	(36.9–73.4)	**157.6**	(146.2–170.5)
61.6	(41.8–88.4)	**173.6**	(158.1–186.7)	**18.0**	**52.0**	(37.6–73.5)	**157.8**	(146.6–170.6)

Figures in bold denote 50th percentile while figures in parentheses denote lowest (3rd percentile) and highest (97th percentile) for respective age and sex.

Source: Modified from: Revised IAP growth charts for height, weight and body mass index for 5– to 18–year–old Indian children.

2.5 GROWTH ASSESSMENT AND MONITORING

Growth assessment and monitoring is the essential component of child health surveillance, even in the absence of apparent abnormality.

While *growth assessment* may be considered as one-point process, *growth monitoring* is more important and requires serial data, e.g. weight, to detect changes in growth parameters over a period of time. Growth monitoring helps in early identification of high-risk children for growth-faltering and institute early remedial measures.

Indian Academy of Pediatrics (IAP) recommends periodic growth assessment at – (a) birth, (b) during each immunization visits at 6, 10, 14 weeks and 6, 9 and 15 months, (c) every 6 months from 18 months to 8 years of age and then d) annually during 9–18 years. While weight and length/height must be recorded during all visits, head circumference should be recorded till 3 years, body mass index (BMI) from 6 year onwards and sexual maturity rating (SMR) from 9 year onwards.

Growth assessment is a four-step process including:

a. Recording of appropriate anthropometric growth parameter (*Observed value*).
b. Comparing this observed value with standard or reference growth norms for corresponding age and sex (*Expected value*).
c. Serial recording of assessed parameters (observed values) on growth charts to assess growth velocity.
d. Interpretation and conveying the information to parents as well as suitable remedial action (*growth monitoring and promotion*).

Step I. Selecting and recording appropriate growth parameter, depends on the purpose of assessment. In regular practice, three growth parameters are commonly recorded in children – *weight*, *length/height* and *head circumference*.

Weight is the best indicator of acute growth insult, though rapid fluctuations during health and disease render it unsuitable for long-term growth assessment. It should be measured on a *digital balance* or *beam balance* with minimum accuracy of 20 gm in infants and 100 gm in older children **(Figs. 2.2, 2.3)**. Spring balances, e.g. bathroom scale or salter-spring balance tend to provide false values due to loss of spring elasticity after repeated use and should be avoided.

Length/height is a better indicator of long-term growth, affected only after prolonged illnesses and remains abnormal for a long time after recovery. It should be recorded in recumbent position (length) in infants <2 years using an *Infantometer* **(Fig. 2.4)** and in standing position in older children, using a *Stadiometer* **(Fig. 2.5)**.

Fig. 2.2: Weighing an infant.

- Place the beam/digital balance on a firm and stable surface to avoid toppling while weighing.
- Check the zero error and correct, if necessary, using the calibrating screw.
- Remove clothing, including diapers, of the infant and place him/her in the center of pan.
- Allow the time to stabilize him/her on the pan, to avoid errors due to swaying.
- Read the scale with eyes perpendicular to the display/dial to avoid errors.

Fig. 2.3: Weighing an older child.

- Place the weighing scale on a firm, even and stable surface.
- Check the zero error and correct, if necessary, using the calibrating screw.
- Ask the child to remove heavy cloths/footwear and stand on the platform.
- Read the weight with eyes perpendicular to the display/scale to avoid errors.

Head circumference is an indicator of brain growth and must be recorded till 5 years of age, using a non-stretchable plastic tape with an accuracy of 0.1 cm **(Fig. 2.6)**.

Mid upper-arm circumference (MUAC) is a useful anthropometric parameter for assessment of nutritional status, which should be recorded using a non-stretchable plastic tape with an accuracy of 0.1 cm **(Fig. 2.7)**.

Fig. 2.4: Measuring length (below 2 years) on infantometer.

- Place the infantometer on a firm and stable surface to avoid toppling.
- Place the infant on the platform in supine position, after comforting him/her.
- Position the head gently straight with crown firmly touching the headboard, and an imaginary line from external auditory meatus to lower orbit being perpendicular to the platform.
- Ensure that shoulders, spine and hips are touching the platform with fully extended legs.
- Slide the soleboard to bring in contact with soles at right angle and toes pointing upward.
- Read the length up to 0.1 cm with eyes perpendicular to scale to avoid errors.

Fig. 2.5: Measuring height (above 2 years) on stadiometer.

- Ensure that stadiometer is placed on a firm, even and stable surface.
- Ask to child to remove shoes/hair-braid etc and stand erect on the platform.
- Ask him/her to look straight with head in Frankfurt plane and external auditory meatus with lower border of orbit in a straight horizontal line.
- Ensure that heels, buttocks, shoulder and back of the head are in same line, touching the scale.
- Slide down the headboard/stick down to bring it in firm contact of the crown.
- Read the length up to 0.1 cm with eyes perpendicular to the scale to avoid errors.

Fig. 2.6: Measuring head circumference.

- Ensure that baby is comfortable in mother's lap or sitting/standing quietly.
- Encircle the measuring tape around forehead to simultaneously touch the nasion anteriorly and inion posteriorly.
- Pull the tap gently to overlap both ends in parietal region and read the measurement at cross-over point (Cross-over technique).

Fig. 2.7: Measuring mid-upper arm circumference.

- Palpate and mark two landmarks on the right arm—Tip of acromion process of scapula and olecranon process of ulna.
- Mark the mid-point of arm between these two landmarks, using a measuring tape/scale.
- Encircle the measuring tape perpendicular to the long axis of arm at this mid-point, gently compressing the muscles.
- Pull the tape gently to overlap both ends and read the measurement at cross-over point (Cross-over technique).

Other anthropometric parameters may be recorded in selected cases to assess nutritional status (skin fold thickness), or investigate cause of short stature (body proportions, bone age), etc.

Step II. Comparing these observed values with standard or reference norms: Observed anthropometric value of the child under assessment are then compared with corresponding expected values in normal children of the same age/gender, using WHO standard norms for those < 5 years of age and IAP reference norms for those 5–18 years, discussed in chapter 2.4.

While this comparison may be done directly using growth tables, it is always preferable to plot individual observed values on appropriate growth charts not only for quick comparison but also to monitor the growth velocity over time by drawing the child's personal growth curve.

To plot the actual measurements on growth chart, following steps are required:

- Select the age and gender appropriate WHO/IAP chart from the parameter under assessment, e.g. weight.
- Plot the observed value of child on this chart as a dot, aligning with X and Y axis.
- Compare the location of this dot (observed value) with the expected value on standard/reference percentile or Z-score curves above and below the value and read as, e.g. *between 25th and 50th percentile or 1 and 2 Z-scores*.
- An observed value between 3rd and 97th percentile of the reference curve, roughly corresponding with (± 2 Z or SD scores) is considered as normal, while values beyond this range are most likely abnormal. Values below –3 Z or SD score indicate more severe abnormality **(Fig. 2.8A to C)**. However, for head circumference, a value <-3Z or SD score is considered as abnormal, i.e. microcephaly **(Fig. 2.8D)**.

Several mobile applications are also available at present to directly compare the observed anthropometric values in a child and plot his/her growth curve, with WHO/IAP reference norms.

Step III. Serial record of assessed parameters on growth chart aims to evaluate the trend of growth over a period of time and identify a deviation from normal growth as early as possible, even in children with previous borderline values. This objective is achieved by plotting the serial anthropometric values on a *growth chart* and joining all the dots to develop a child-specific growth curve.

Location and shape of this *child's growth curve* as compared to *reference curves* provides important information about the trend of growth in child under assessment. Any child's growth curve, which runs flatly below the lowest reference curve or plateaus/dips after initially being above the reference curve is a cause of concern.

Growth velocity is defined as *"rate of growth or change in a growth parameter over unit period of time."* For example, since length at birth is 50 cm and at one year is 75 cm, growth velocity in first year is 25 cm/yr. Growth velocity is not uniform throughout the childhood and a baby has different growth velocity at different ages and for different parameters.

Growth velocity is calculated by serial recording of selected parameter at different time intervals, i.e. monthly or yearly and then dividing the change in parameter by the time, interval. Reference values for different growth velocities at various age intervals are also available, termed as *reference velocity norms* in tabular form and *reference velocity curves* in graphic form.

Step IV. Interpretation of growth records, conveying the information to parents and taking suitable remedial actions: The main objective of growth assessment is not only to detect the growth abnormality, but also to make the mother (and family) realize its significance and take timely action. This process of continuous check and timely action is strategically described as *growth monitoring and promotion*, discussed later.

Growth monitoring and promotion (GMP): Growth monitoring aims not only to track the growth of a child over time but also to enable mother/caregiver to visualize growth or lack of growth in their children and to provide specific, relevant and practical guidance for remedial measures, also termed as growth monitoring and promotion).

While WHO/IAP growth charts may be used for growth monitoring in facility setting, many simplified growth charts are also available for field use, including the widely popular one "Road-to-health card". However, recently, *Mother-to child protection card* has replaced most of them, being used routinely in all national health programs.

Mother to Child Protection Card

Since the adoption of WHO growth standards in 2009, a new *mother and child protection card* has been developed under National Health Mission, which also includes two gender-specific growth charts for boys and girls below 3 years of age **(Fig. 2.9A and B)**.

These charts have three differently colored zones based on weight-for-age as per WHO standard norms – top green zone between 50th percentile and – 2 SD values (***normal***), second yellow zone between –2 SD and –3 SD values (***underweight***) and bottom red zone for values <– 3 SD (***severe underweight***).

In addition, these cards also serve as immunization card, development charts (Ch 2.7) and provide parenting tips, e.g. breastfeeding, weaning, etc.

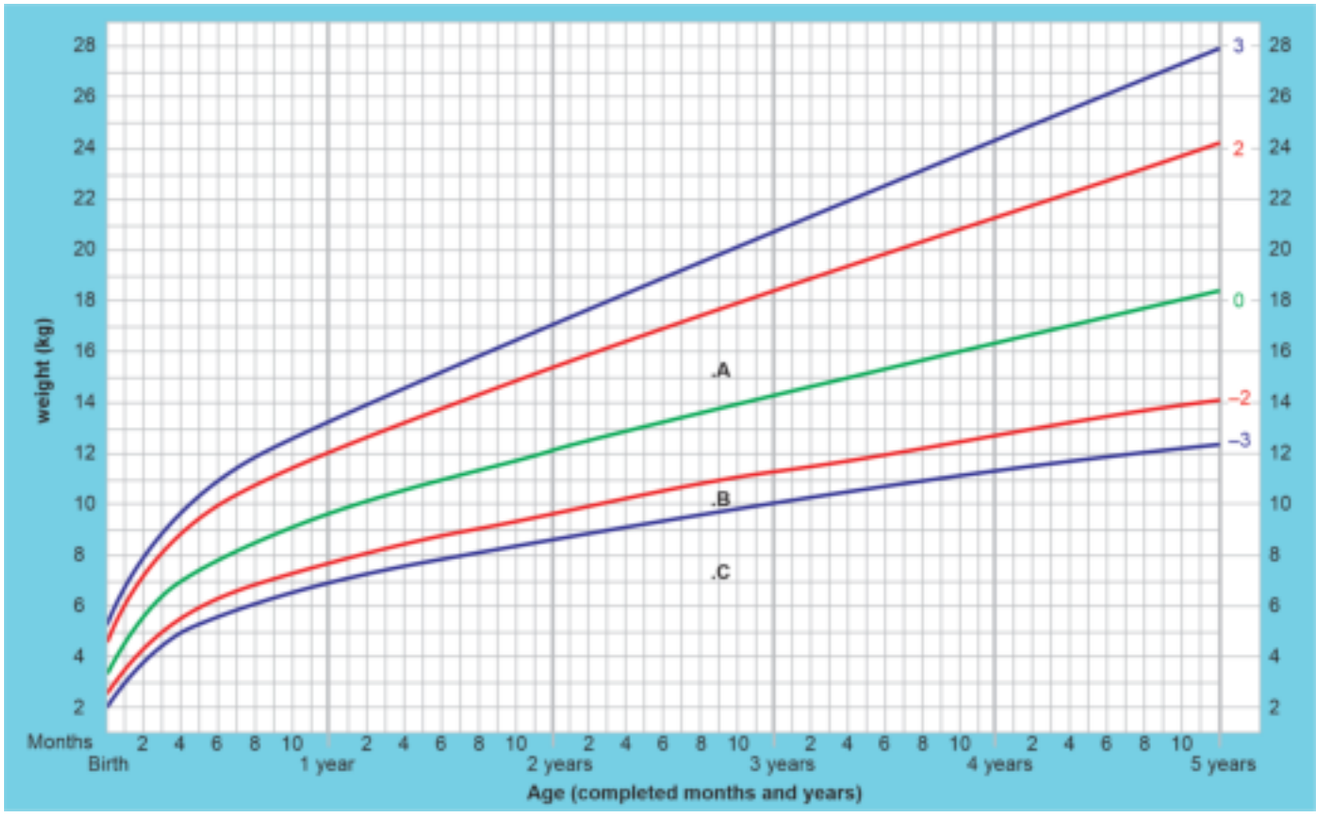

Fig. 2.8A: **Interpretation for weight for age (WFA). A:** Normal, **B:** Undernutrition, **S:** Severe undernutrition

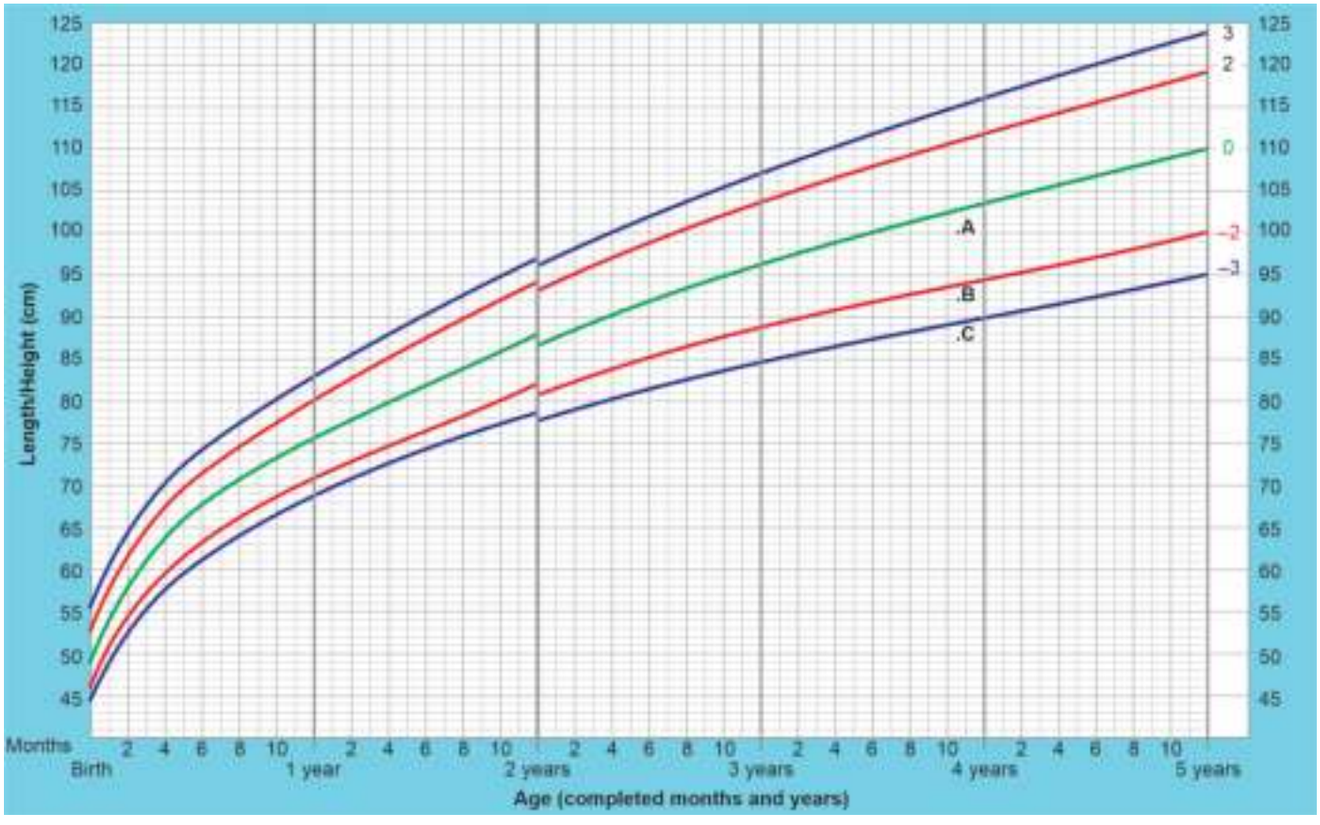

Fig. 2.8B: **Interpretation for length/height for age (L/HFA). A:** Normal, **B:** stunted, **C:** Severely stunted

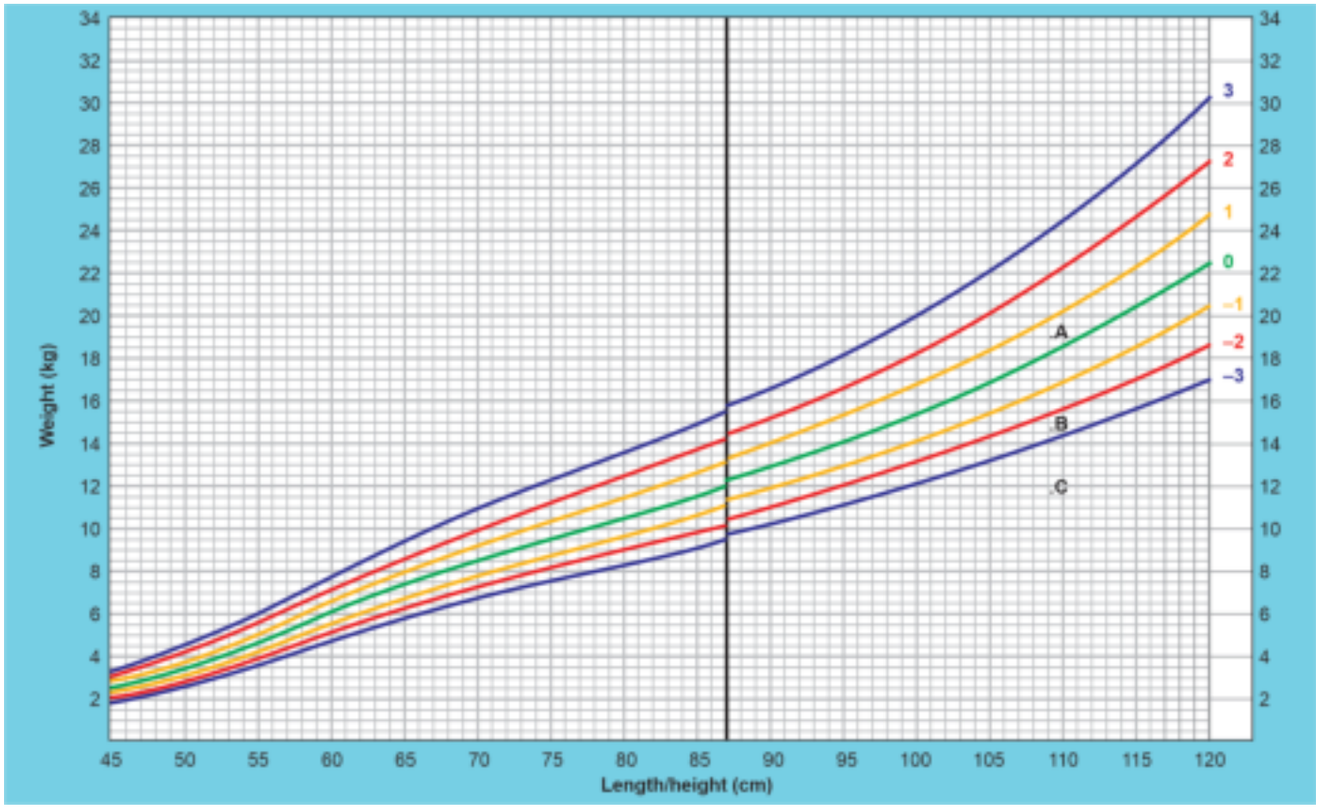

Fig. 2.8C: Interpretation for weight for length/height (WFL/H). A: Normal, **B:** Wasted, **S:** Severely wasted

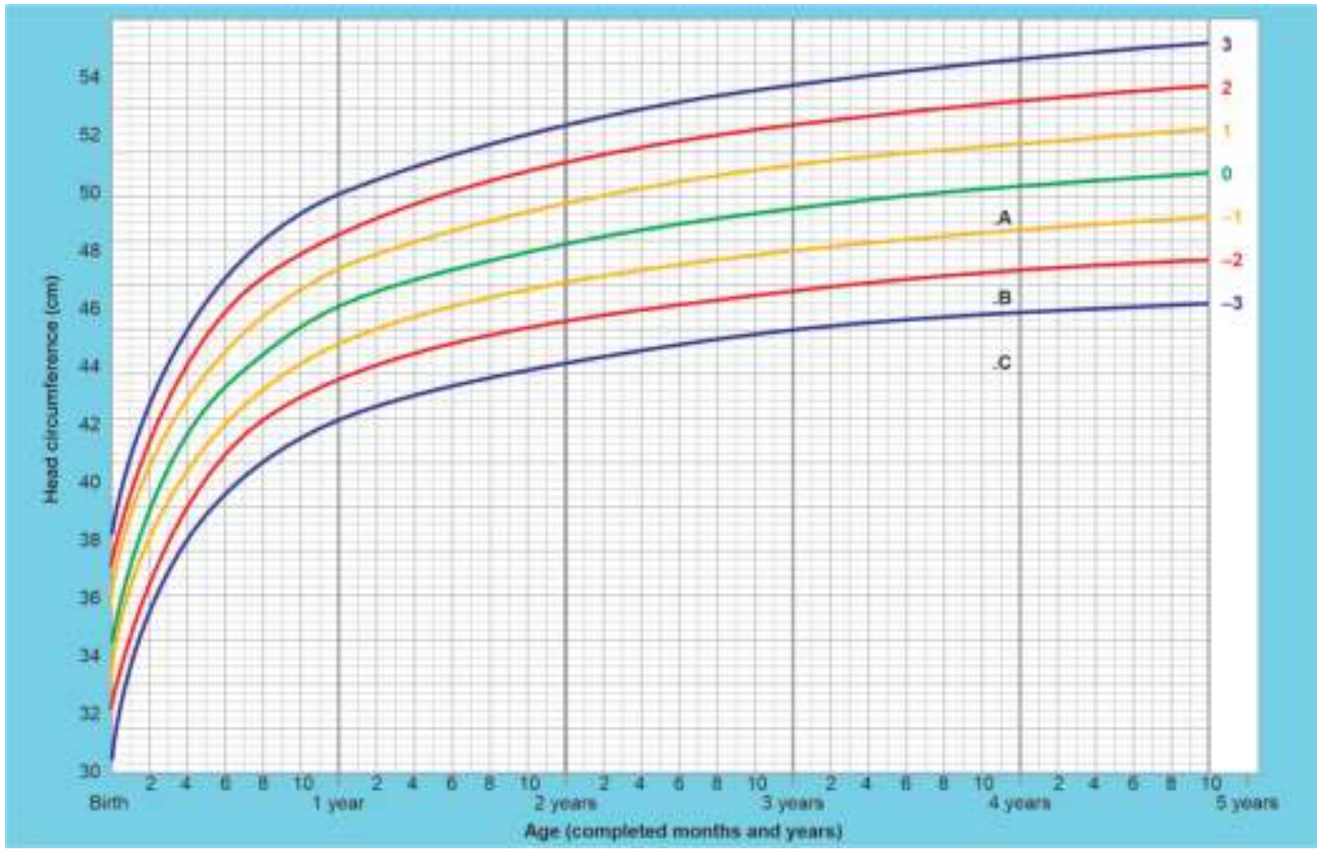

Fig. 2.8D: Interpretation for head circumference. A: Normal, **B:** Borderline, **C:** Microcephaly

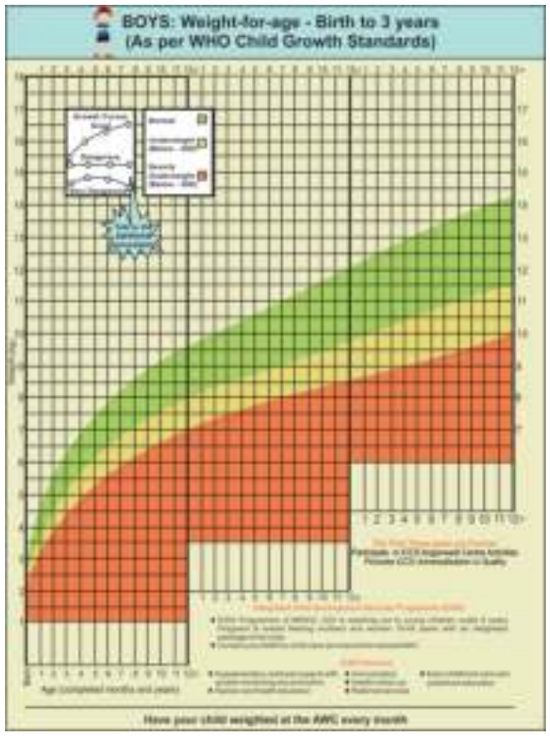

Fig. 2.9A: **Mother to child protection card (boys).**

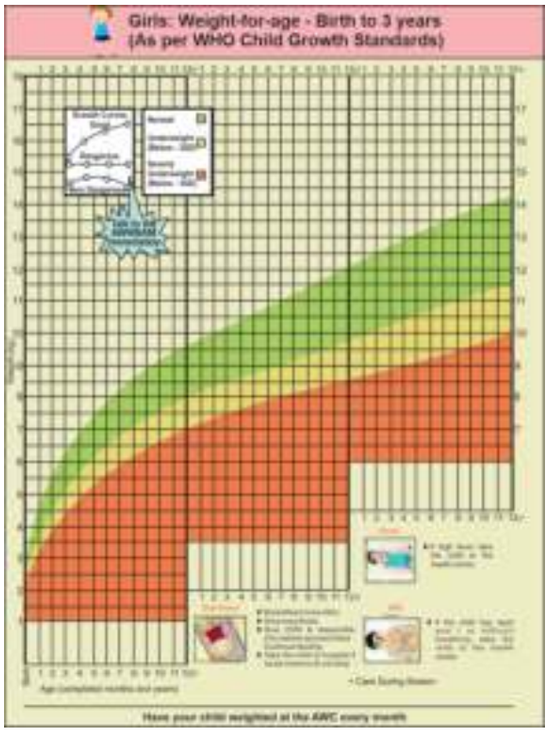

Fig. 2.9B: **Mother to child protection card (girls).**

2.6 NORMAL CHILDHOOD DEVELOPMENT

Development denotes *physiological or functional maturation of various organs or systems, acquisition of newer functions or skills and adaptation to the environment.* While it is multi-dimensional process, the term development is popularly used in connection to neurological and psychosocial maturation.

Factors, which affect growth, also affect development (Ch 2.1). However, two most important factors for appropriate development are – (a) normal brain growth and (b) adequate emotional stimulation.

Most critical period for brain growth extends from mid-gestation till 2 years of age, characterized by explosive growth in neuronal cells, neuroglial proliferation and progressive myelination. Nearly 90% of brain growth is complete by two years of age. Any neurological insult during early childhood, e.g. hypoxia, infections or trauma, often leaves severe and irreversible neurological sequelae.

Emotional stimulation is another major determinant of development in early childhood, dependent on many factors, e.g. parenting practices, exposure to abuse and violence, institutionalization, etc.

Early Childhood Development (ECD)

The term *early childhood development* refers to physical, cognitive, social-emotional and linguistic development during early childhood, specially in *first three years of life*, which determines the learning outcomes in later life.

Nurturing care for ECD refers to the five components of care during first three years of life to achieve optimal development, including: *(1) good health, (2) appropriate nutrition, (3) safety and security, (4) responsive parenting, and (5) early learning opportunities*.

2.6.1 GENERAL LAWS (PRINCIPLES) OF DEVELOPMENT

Like growth, development also follows the laws discussed earlier in Chapter 2.2, as follows:

- **Development is a continuous and qualitative process,** starting from conception and continuing till maturity or even beyond. However unlike growth, precise measurement of development is difficult as a baby may be able to perform the same milestone, e.g. sitting, with variable degrees of maturity at different ages. Developmental assessment consist not so much of observing *what* a child does, but *how* he does it.
- **Development progresses in cephalocaudal direction,** head control is achieved earlier than sitting and further followed by standing. Fine motor functions generally mature from proximal to distal manner, e.g. voluntary lifting of hands to reach-out for an object appears before development of fine finger movements to grasp it, e.g. pincer-grasp.
- **Individual pace of development is variable and unique for every child.** Some children are *rapid-developers*, while others are *slow-developers*. Hence, it is important to exercise caution, before declaring a child as developmentally delayed.

Further, pace of development may also differ in different domains, e.g. gross-motor, fine-motor, psychosocial and language. Some children develop slowly in certain fields and faster in others. However, significant differences in development among different domains are abnormal and are termed as *developmental dissociation*. Generally, girls have a faster speech development, while boys develop faster in motor fields.

- **General sequence of achieving developmental milestones is fairly consistent**, despite individual variations in the pace of development. It is extremely unlikely to achieve a later milestone, e.g. sitting, until the earlier milestone, e.g. neck holding, has been achieved.
- **Disappearance of primitive reflexes is also a part of development:** Certain primitive neonatal reflexes, e.g. grasp or stepping reflex, must disappear before the corresponding voluntary function, e.g. voluntary grasp or standing is achieved. Persistence of a neonatal reflex beyond the expected age of its disappearance, by itself indicates developmental problem, as seen in cerebral palsy.
- **Generalized mass activity is gradually replaced by more specific and purposive response,** e.g. while an infant of 3–4 months squeals and excitedly moves all the limbs when offered a toy, an older child may simply smile and reach-out to it with one hand.

2.6.2 DEVELOPMENTAL MILESTONES

Neurological development is assessed in terms of the *milestones*, i.e. *easily identifiable events representing maturation of certain physical functions*, e.g. sitting or smiling, which are expected to be achieved by a normal child within certain age limits. Milestones may be broadly divided into five major domains:

1. *Gross motor* milestones, e.g. sitting, standing, etc.
2. *Fine motor* milestones, e.g. handling of objects, feeding himself, etc.
3. Personal-social milestones, e.g. interacting with others, expression of emotions, etc.
4. Adaptive (Cognitive) milestones, e.g. ability to explore environment and learn from experiences.
5. *Linguistic* milestones, e.g. development of speech.

A. Gross motor milestones reflect maturation of locomotor functions and require normal neurological development as well as adequate muscle mass and tone. These functions may be delayed in grossly malnourished children, despite adequate neurological functions.

While lifting the chin momentarily from bed in prone position is the earliest recognizable gross motor milestone (4 weeks), persistent neck (head) holding is not achieved before 3 months and may be considered as the first key gross motor milestone for practical purpose.

TABLE 2.7: Key gross motor milestones

Age	*Gross motor milestone*
1 mo	Lifts chin momentarily in prone position
3 mo	Neck-holding
4 mo	Roll-over from supine to prone position
5 mo	Roll-over from prone to supine position
6 mo	Sits with support (Tripod position)
8 mo	Sits without support
9 mo	Crawls, pulls to stand
10 mo	Stands with support, creeps
12 mo	Walks without support
15 mo	Walks, creeps upstairs
18 mo	Runs, walks backward
24 mo	Walks up and down-stairs (two-feets/step)
36 mo	Rides tricycle, climb stairs one-foot/step
48 mo	Hops on one foot, goes down-stairs one-foot/step
60 mo	Skips with both feet

Table 2.7 enlists key gross-motor milestones till 5 years of age.

B. Fine motor milestones reflect development of certain fine skills, required for day-to-day functions like play, eat, draw, etc. These milestones are more reliable indicators of neurological maturity, as such skills are governed by large cerebral area and usually not affected in nutritional disorders. Isolated delay in maturation of these milestones indicates cerebral palsy or peripheral nerve injury, e.g. Erb's paralysis.

Important components of fine motor development in order of maturity include – (i) hand-eye coordination, e.g. reaching out for objects, (ii) hand coordination, e.g. grasping an object voluntarily, (iii) hand-hand coordination, e.g. transfer of objects, and (iv) hand-mouth coordination, e.g. feeding himself/herself.

Holding an object when offered in hand (voluntary grasp) at 4 months of age may be considered as the earliest and easily identifiable fine motor milestone, which is possible to achieve only after disappearance of neonatal grasp reflex. **Table 2.8** enlists key fine-motor milestones till 5 years of age.

C. Adaptive milestones, also termed as *cognitive milestones*, denote the development of the ability to explore environment and learn from new experiences. Achievement of adaptive milestones needs normal cognitive functions as well as normal special senses, e.g. vision and hearing.

Visual fixation to a moving object (4–6 weeks) may be considered as the earliest adaptive milestone, checked by observing infant's eye movements in response to a bright moving object, e.g. a red-ring tied to a string. Other adaptive milestones include visual exploration (hand-regard) or oral exploration of body parts (mouthing) and learning from experiences, e.g. searching for a hidden toy

TABLE 2.8: Key fine motor milestones

Age	*Fine motor milestone*
4 mo	Voluntary grasp (hold objects when given),
5 mo	Bidextrous reach for an object (both hands)
6 mo	Unidextrous reach, transfer of objects between hands
9 mo	Immature pincer-grasp (probes with forefinger)
10 mo	Mature pincer-grasp, release of object on request
12 mo	builds tower of 2 cubes
18 mo	Scribbles, tower of 3–4 cubes
24 mo	Tower of 6 cubes, imitates vertical and horizontal lines
30 mo	Tower of 8 cubes
36 mo	Tower of 8–10 blocks, copies 'circle'
48 mo	Builds bridge, copies 'cross'
60 mo	Copies 'Triangle'

TABLE 2.9: Key adaptive (cognitive) milestones

Age	*Adaptive (Cognitive) milestones*
4 wks	Fixes vision on moving object up to 45°
2 mo	Follows a moving person
4 mo	Hand-regard, excited to see a toy/food
5 mo	Mouthing, hand-regard disappears
6 mo	Searches for a dropped toy
8 mo	Finds partially-hidden objects
12 mo	Mouthing stops, looks at pictures
15 mo	Turns 2–3 pages at a time
18 mo	Turns single page at a time
24 mo	Points to 4–6 body parts, matches shapes
36 mo	Knows name and gender
48 mo	Right-left discrimination
60 mo	Counts till 10, identifies coins

or matching the shapes. **Table 2.9** enlists key adaptive milestones till 5 years of age.

Many adaptive milestones tend to disappear after the learning process is complete. *Hand-regard*, i.e. exploration of own hand appears at 3–4 months and disappears by 6 months **(Fig. 2.10)**. Similarly, mouthing appears at 5–6 months and disappears by the end of infancy. Persistence of hand-regard beyond 6 months or mouthing beyond 12 months suggests delayed neurological development.

D. Psychosocial milestones, i.e. development of interpersonal relationship and social skills, depend on higher cerebral functions as well as external inputs, e.g. normal vision and social stimulation. Social smile (~6 weeks) may be considered as the earliest psychosocial milestone. **Table 2.10** enlists key psychosocial milestones till 5 years of age.

Isolated delay in these milestones indicates intellectual disability, autism, visual impairment and emotionally deprived child, e.g. orphans.

Fig. 2.10: Hand regard.

TABLE 2.10: Key personal-social milestones

Age	*Personal-social milestones*
6 wks	Social smile
3 mo	Recognizes mother
4 mo	Smiles at mirror image
6 mo	Stranger's anxiety, enjoys 'peek-a-boo'
9 mo	Waves 'bye-bye'
12 mo	Responds to name, plays simple ball game, parallel play
15 mo	Jargon, points to desired object
18 mo	Domestic mimicry (copies parents, e.g. sweeping)
24 mo	Dry by day, asks for food, show toys to others
30 mo	Washes hands, brushes teeth
36 mo	Dry by night, share toys
48 mo	Goes to toilet alone, group-play
60 mo	Dresses/undresses independently

TABLE 2.11: Key Linguistic milestones

Age	*Linguistic milestones*
6 wks	Turns head towards sound
3 mo	Makes cooing sounds
4 mo	Laughs aloud
6 mo	Says monosyllables (ma, da)
9 mo	Says bi-syllables (mama, dada)
12 mo	Speaks with vocabulary of two meaningful words
18 mo	has vocabulary of 8–10 words
24 mo	Speaks 2–3 word sentences, uses pronouns (I,You)
36 mo	Asks questions, tells name and gender
48 mo	Sing songs, tells stories
60 mo	Speaks grammatically correct sentences

E. Linguistic milestones require normal hearing, normal central functions as well as healthy organs of phonation. Hearing impairment is the most common cause of delayed language development. Startle response to a sudden sound in newborns suggests hearing ability. Appearance of monosyllables (6 months) may be considered as earliest proper linguistic milestone, though a younger infant is also able to make non-specific vocalizations, e.g. cooing sounds or laughs aloud. **Table 2.11** enlists key linguistic milestones till 5 years of age. Some other important aspects of language development are also discussed in Chapter 3.8.

It is re-emphasized that pin-pointing the precise age of appearance for a particular milestone is neither possible nor desirable, due to continuous maturation of these functions.

2.7 DEVELOPMENTAL ASSESSMENT

Developmental assessment is an integral part of every child's health check-up, even if apparently normal. However, it is not necessary to perform exhaustive developmental assessment in every child and the depth of assessment must vary, according to perceived risk of abnormality.

In practice, developmental assessment must be conducted in a step-wise manner, as follows:

a. Informal *developmental surveillance* of all children during health care visits;
b. *Development screening* of all children at scheduled intervals;
c. *Formal developmental assessment* in children with abnormal screening results.

This chapter deals with *informal developmental surveillance* of all under-five children during regular well-baby clinic/immunization/health-care visits, as well as *development screening* of all children at scheduled age-intervals, in order to identify children who need in-depth formal assessment, discussed in Ch 3.5.

Development surveillance is a continuous and informal process, not to draw a line between normal and abnormal, but merely to identify high-risk children, who need referral for early developmental screening and/or follow-up. Three important components of informal development surveillance include:

- *Ask the* parents about age of achieving milestones (developmental history);
- *Observe the* baby's performance and behavior in the clinic (developmental observation);
- *Elicit* common age-appropriate milestones (developmental examination).

Developmental history must be obtained by a reliable caretaker, preferably mother, to find out the age of achieving common milestones in different domains, with following principles:

- Record achievement of various milestones in all domains with the age of attainment.
- Compare actual age of attainment with expected age of attainment **(Table 2.8 to 2.12)** with due consideration for normal variations. In preterm, corrected age should be used to assess adequacy of milestones till the end of infancy.
- Denote the results as developmental age in different fields separately, rather than averaging out to calculate developmental quotient on this informal assessment.
- Record all milestones sequentially, starting from neonatal period irrespective of the age, in cases with suspected neurodevelopmental problems to get an idea about the age from which milestones began to falter.

However in apparently normal children, it is time-saving to begin with last few milestones that the child should have achieved at present chronological age in each domain and go backwards *only* if the last expected milestone/s have not been achieved.

- In cases with abnormal development, find out if a milestones was never achieved (Delay) or has been lost after the initial achievement (Regression). Regression of milestones is an important clue to neurodegenerative disorders.

Mother and child protection (MCP) card, used by ASHA/Anganwadi workers throughout India, includes a simple tool for monitoring of the child's development. On this card, ASHA/AWW/other field health workers have to simply mark a tick or cross against the pictorially depicted milestones at different ages (2–3, 4–6, 7–9, 10–12, 18, 24, and 36 months). This chart also provides parenting tips to stimulate development as well as red-flag signs **(Table 2.12)** to identify children for referral for formal developmental assessment.

Developmental observation involves observing the child's behavior and interaction with others while waiting in the clinic or approached by mother/doctor. Some important milestones which can be assessed by simple observations are as follows:

- *Observe an infant from a distance in the waiting room* for behavior for *personal-social milestones*, e.g. social smile (6 weeks), eye-contact (3 months) enjoys mirror image (4 months) hand-regard, (4–6 months) mouthing (5–12 months), searching for a dropped rattle/toy (6 months), attempting to find a partly-hidden toy (8 months) and waving *bye-bye* (9 months).
- *Observe an older child while playing for interaction with others*, e.g. enjoying peek-a boo (6 months), plays/throws ball (12 months), parallel play despite presence of other children (12 months), pointing to a desired toy or object (15 months), mimicry (18 months) showing toys to others (24 months) and sharing toys with others (36 months).
- *Observe for gross-motor milestones*, e.g. sitting with/without support, standing with/without support. Crawling/creeping, walking, going up/down stairs, etc.
- *Observe when approached by mother/others, e.g.* excitement with limb movement when approached by mother, i.e. recognition of mother (3 months) or crying when approached by the examiner, i.e. stranger anxiety (6 months), etc.
- *Listen him/her for linguistic milestones* cooing sounds (3 months), laugh aloud (4 months), monosyllables (6 months), bisyllables (9 months) jargon (15 months), two meaningful words (12 months), 8–10 meaningful

TABLE 2.12: Red-flag signs for development delay on informal developmental surveillance*

At 3 months	***At 6 months***
No social smile	No head control
No Startle response to sounds	Cannot sit up with support
No eye to eye contact when fed/ cuddled	Does not grasp things within reach
Persistent squinting >2 months	Does not track a moving object with head/eyes
Persistent limb stiffness/arching of head	Does not vocalize, e.g. *'ah, ..eh, ..oo..'*
Cortical thumb	Unable to raise head in prone position
At 9 months	***At 12 months***
No roll-over	No pincer-grasp
Cannot sit without support	Does not stretch hands to be picked up
Does not turn towards the sound (Out of sight)	Does not respond to own name
Does not utter monosyllables, e.g. *'ma.. pa.. ba'.*	Does not search for half-hidden toys
Tilts head always to one side, whenlooking at objects	Does not play social games, e.g. Peek-a-boo
At 18 months	***At 24 months***
Cannot stand without support	Does not walk steadily while pulling a toy
No response to gestures, lives in *own world*	Does not respond to gestures. e.g. *bye-bye*
Cannot put small objects in a container	Cannot scribble
Does not use both hands for everyday activity	Does not point to body parts
Does not point finger to a named object,	Does not use two word phrases – *'give milk'*
Does not say single words, e.g. *'mama, papa'*	Does not understand/ follow simple instructions
At 36 months	
Has troubles climbing up/down stairs	
Cannot play "pretend" games	
Cannot eat without help	
Continuous drooling/ unclear speech	
Does not communicate meaningfully, repeats others' speech	
Does not speak simple 3-word sentences, e.g. *'mummy give milk'*	

*Based on Mother and Child protection card (MCP)

words (18 months), 2–3 word sentences (24 months) and complete sentences (60 months).

Developmental examination of a young child is tricky and must be performed before the systemic examination, when child is playful and not apprehensive. Information already obtained by developmental history (if reliable) and simple observation needs not be elicited. No rigid pattern should be followed for developmental examination, which may begin informal assessment of vision and hearing, eliciting fine motor and adaptive/cognitive milestones and lastly, gross-motor milestones, which might disturb the child. A short list of items required for developmental assessment is given in **Table 2.13**.

TABLE 2.13: Development assessment kit

- Red ring on a string (6–7 cm diameter)
- Small bell
- Paper pellets
- Nine red cubes ~1'' each
- Paper and crayon
- Picture-book with thick pages
- Doll and mirror
- Plastic cup with spoon (Small)
- Shape-board with common shapes

A tentative protocol of developmental examination of a child is as follows:

- *Elicit or check vision* by dangling a red-ring attached to a string in the visual field (follows till 45° at 4 weeks and 180° at 8 weeks), and following the mother's movement (2 months)
- *Elicit or check hearing* using a small bell for turning the head towards sound (6 weeks) or response to the name-call (12 months).

Fig. 2.11: **Pincer grasp.**

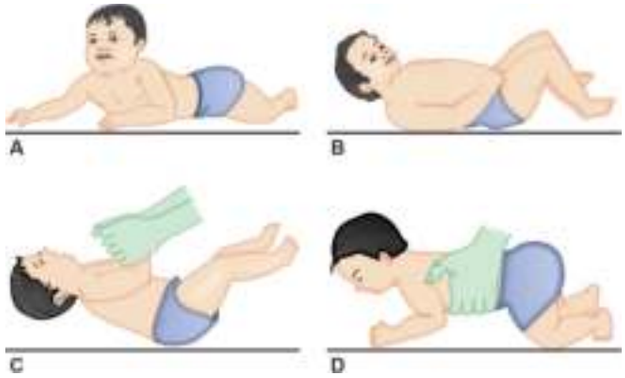

Fig. 2.12: **Head holding in different positions. (A) Prone position; (B) Supine position; (C) Pull to sit position; (D) Ventral suspension.**

- *Elicit fine motor milestones* in an infant by:
  - Offer a red ring to observe for voluntary grasp (4 months), bidextrous approach with both hands (5 months) unidextrous approach with one hand (6 months), transfer of object (6 months) and release of object on request (10 months).
  - Offer a paper pellet to observe for the maturity of pincer grasp (9–10 months) **(Fig. 2.11)**.
- *Elicit fine motor milestones in an older child* by:
  - Offer a cube to see stacking, e.g. tower of 2 cubes (12 months), 3 cubes (18 months), 6 cubes (24 months) 8 cubes (30 months), 9–10 cubes (36 months) and making a bridge (48 months).
  - Offer a paper and crayon to see for scribbling (18 months) and imitating vertical/horizontal lines (24 months), circle (36 months), cross (48 months) and triangle (60 months).
  - Offer a bright picture-book with thick pages to see whether he looks at pictures (12 months), turns 2–3 pages at a time (15 months) or turns single page at a time (18 months)
  - Check/ask mother for the ability to feed with a spoon (15 months) or cup (18 months), pulling out of shoes (18 months), attempts to undress (24 months), brush (30 months) and helps to dress (36 months).
- *Elicit adaptive/cognitive milestones* by:
  - Ask him/her to point body parts (18–24 months), name and gender (36 months), right/left side discrimination (48 months), to sing a nursery rhyme (48 months) or tell a story (48 months) and count up to 10 coins (60 months).
  - Offer a doll and ask to point 4–6 parts of the doll (24 months).
- *Elicit gross-motor milestones by history as well as:*
  - Assess the neck-control in infants <3 months in different positions, e.g. supine, prone, pull-to-sit and ventral suspension **(Fig. 2.12)**.
  - Ask the history or elicit other gross-motor milestones, e.g. roll-over, sitting with/without support, standing, crawling, pulled to sit walking, go up/down stairs, etc.

In addition, thorough physical examination should follow the developmental assessment to search for neuromuscular abnormalities, e.g. abnormal posture, tone or power, etc. and vision/hearing impairment, which might hinder to achieve full potential of development.

Developmental screening: Developmental screening denotes administration of standard, validated and locally appropriate screening tests to identify high-risk children who needs detailed developmental assessment.

IAP recommends that:

a. *All children should be screened using standardized tools at the age of 9–12 months, 18–24 months and at school entry, with timing coinciding with immunization visits, and*
b. *High-risk children should also be additionally screened at 4–6 months.*

Many developmental screening tests are available for screening purpose, including widely used Denver developmental screening test (DDST), or locally developed *Phatak's Baroda development screening test* or *Trivandrum development screening test. Please note that these tests are screening tests and should not be used to assign development quotient/intelligence quotient (DQ/IQ).*

- *Denver development screening test* (DDST) and its modification (DDST II) are widely used to assess development till 6 years of age in four domains—gross motor, fine motor or adaptive, language and personal-social behavior. DDST II contains 125 items of simple nature and a child's development is considered as delayed if he/she cannot perform an item, which can be done by 90% of children with comparable age.
- *Baroda development screening test*, developed in 1991, by Phatak *et al* at child development unit of Baroda University, is an Indian adaptation of *Bayley's scale of infant development (BSID)* to screen children up to 30 months of age. Test assesses child's performance on different milestones (53 items) and is available as

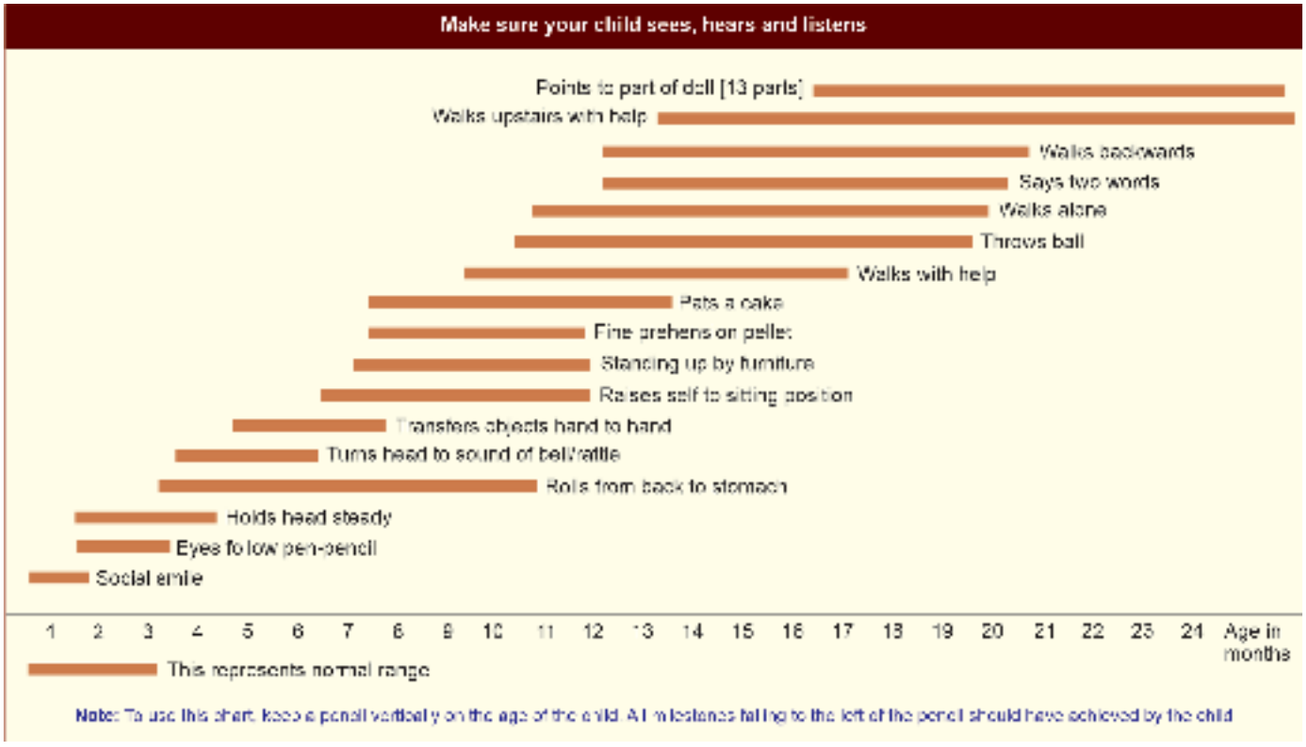

Fig. 2.13: **Trivandrum development chart.**

commercial kit including several objects and tools for the assessment.

- *Trivandrum development screening test*, a simple and most popular development screening test in India, based on Baroda norms, using 17 test milestones **(Fig. 2.13)**. This test provides the upper (97th percentile) age-limits for development of test milestones, beyond which a baby may be considered as developmentally retarded. It is designed for easy to use by community level health worker for mass screening and takes around 5 minutes to complete.

Other commonly used development screening tests include *Age and stage questionnaire* (ASQ-3)- a parent-completed questionnaire, *Rashtriya Bal swasthya Karyakram (RBSK) screening* tool, and Goodenough-Harris *Draw-a-man* test, etc.

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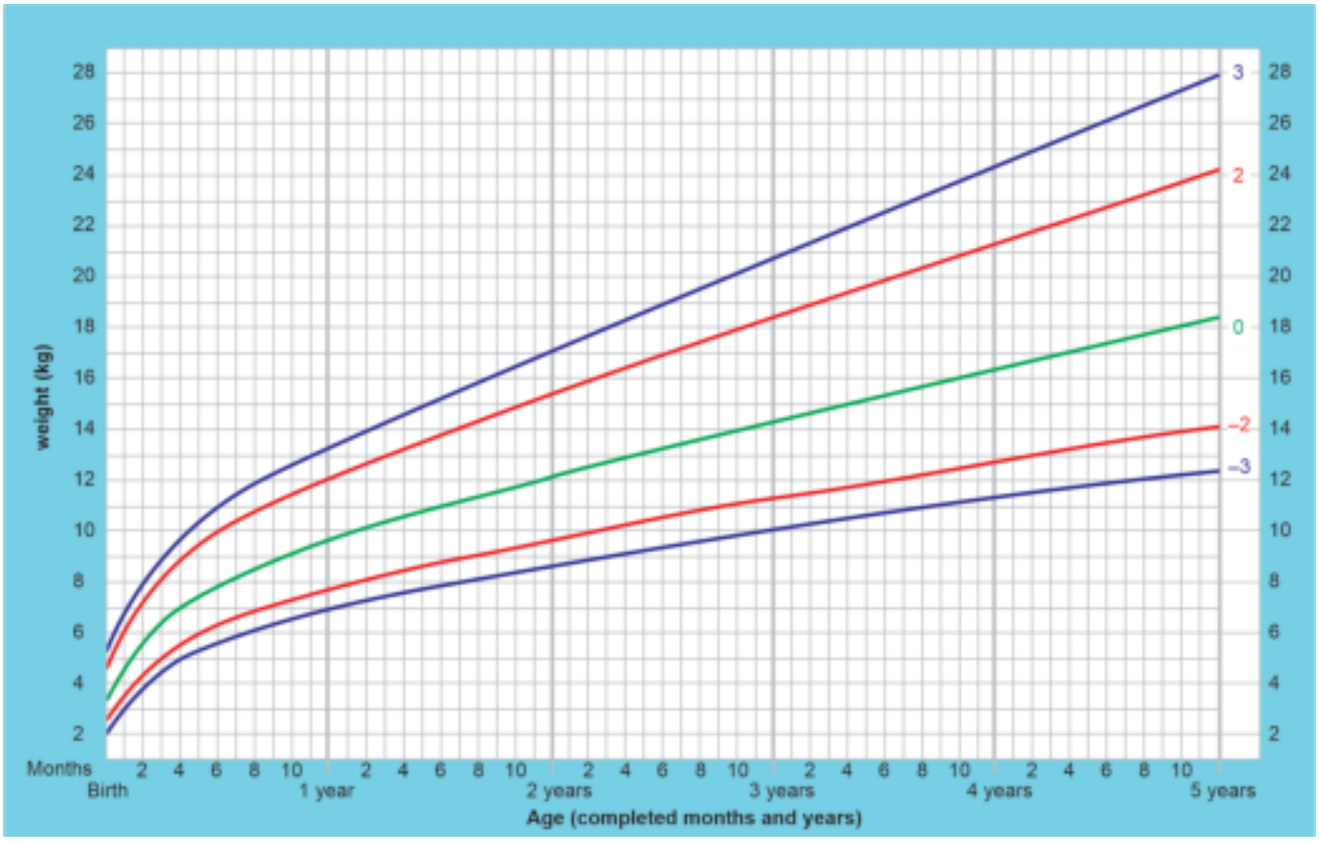
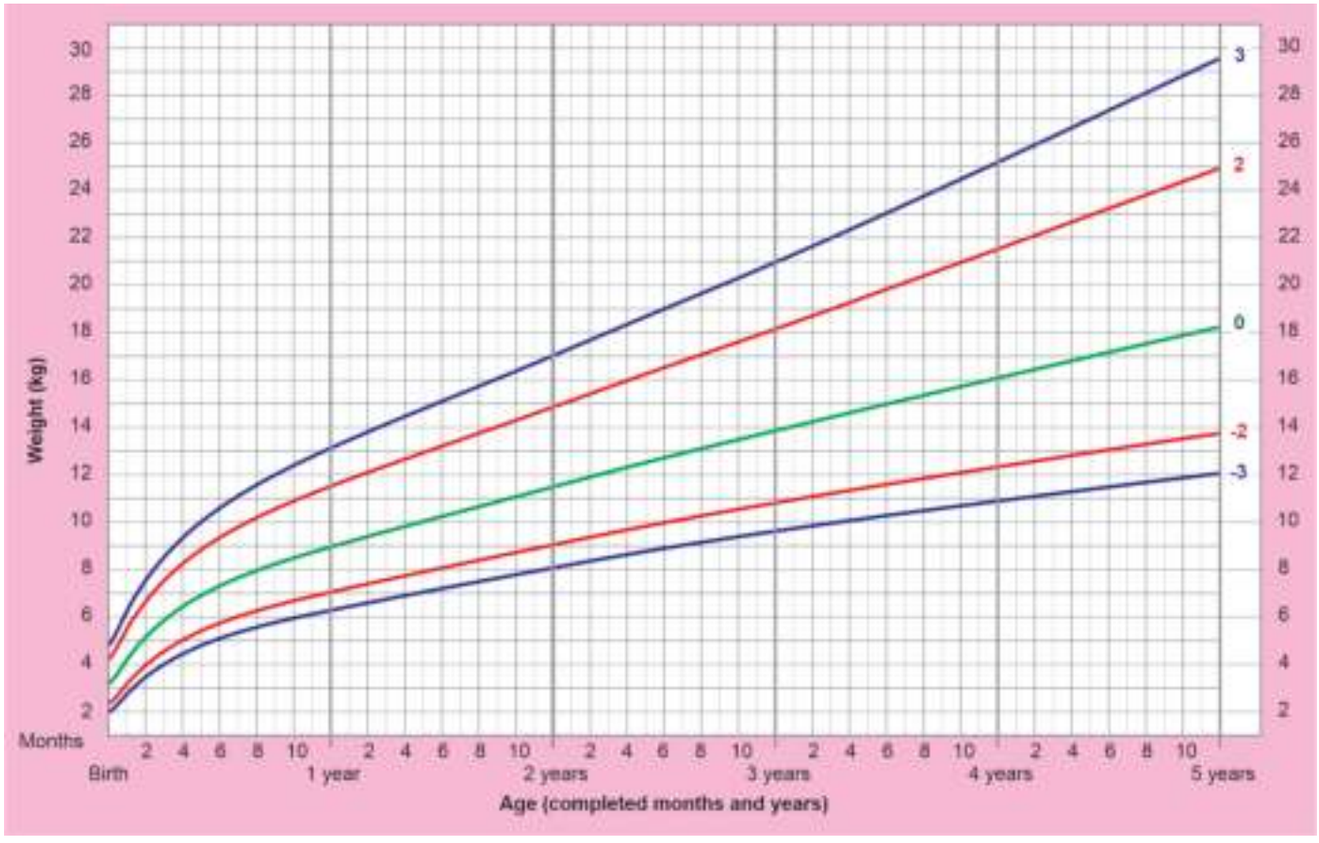
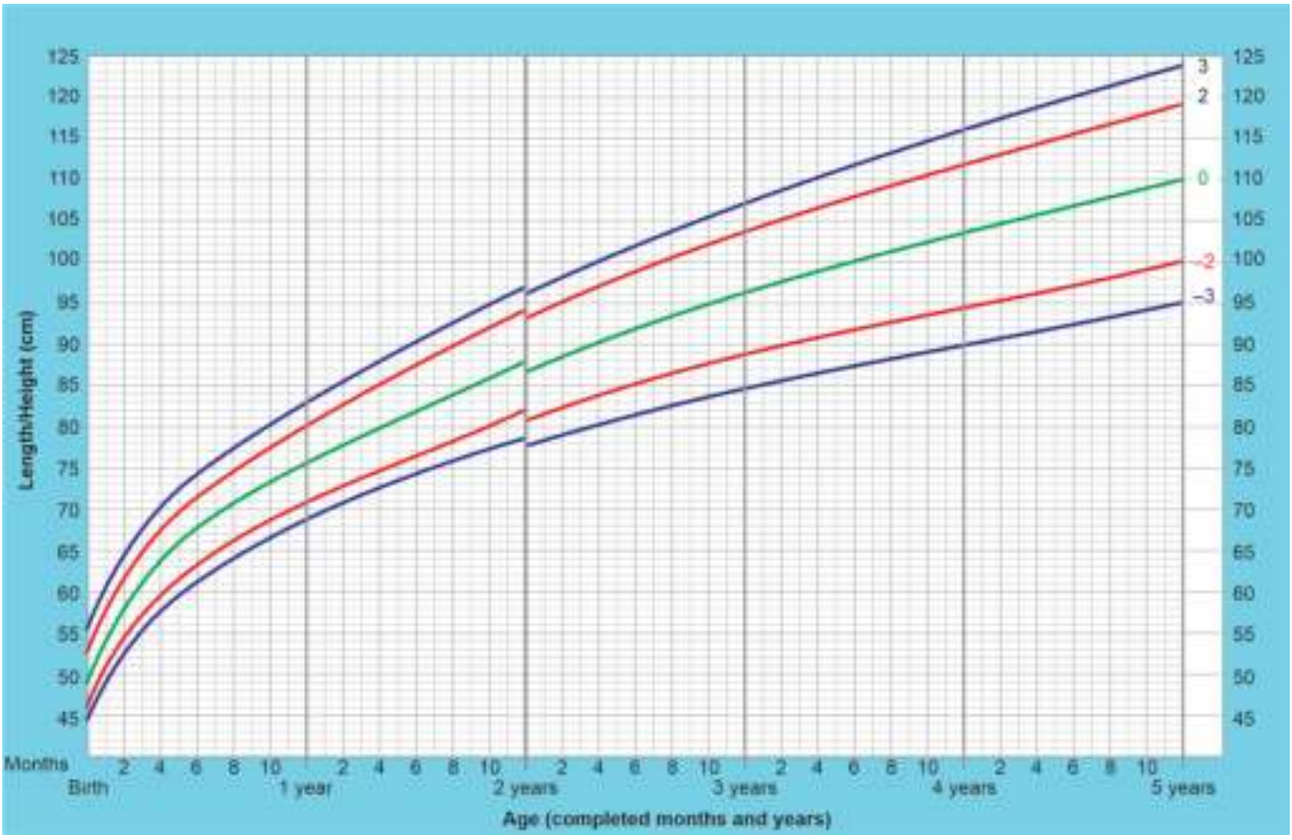


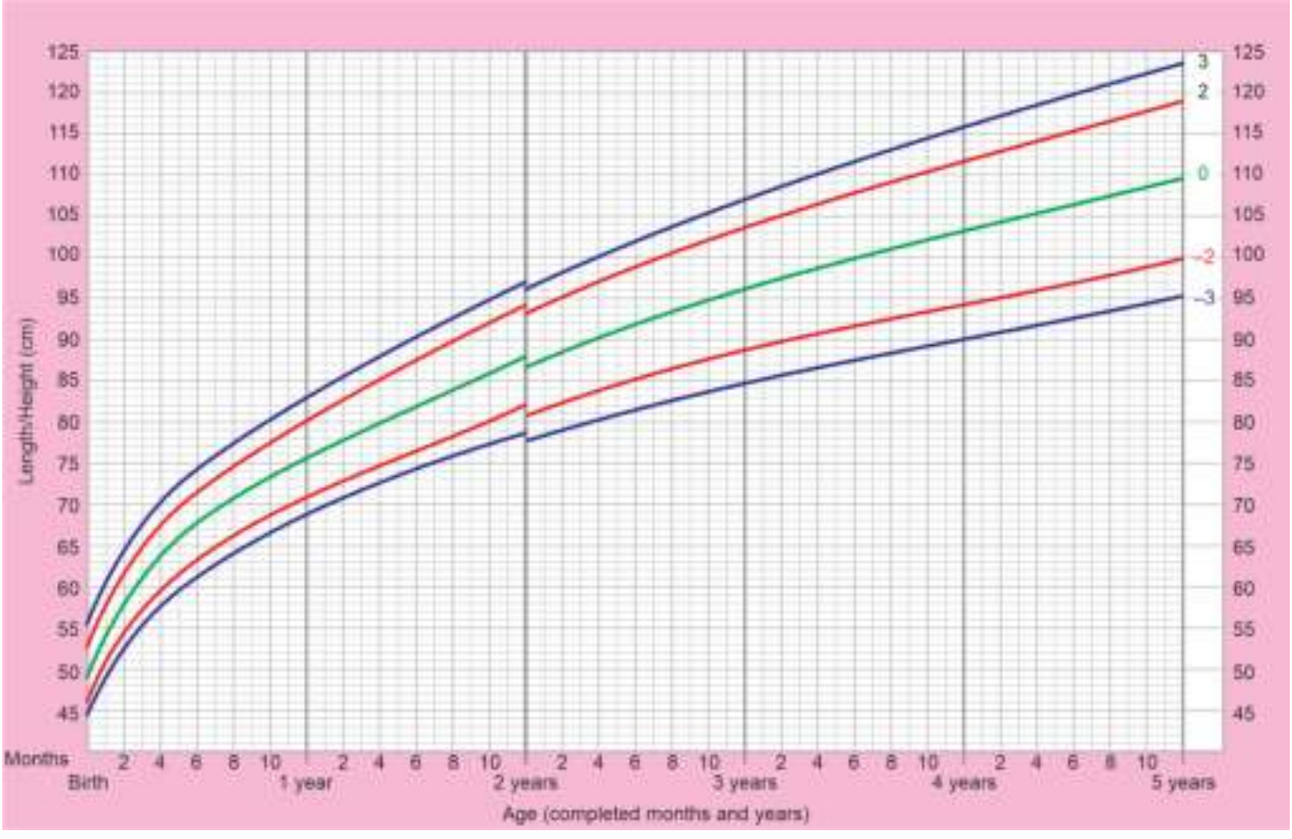
Appendix 2.1: **WHO child growth standards (Z-score): Weight-for-age: Birth to 5 years (boys).**



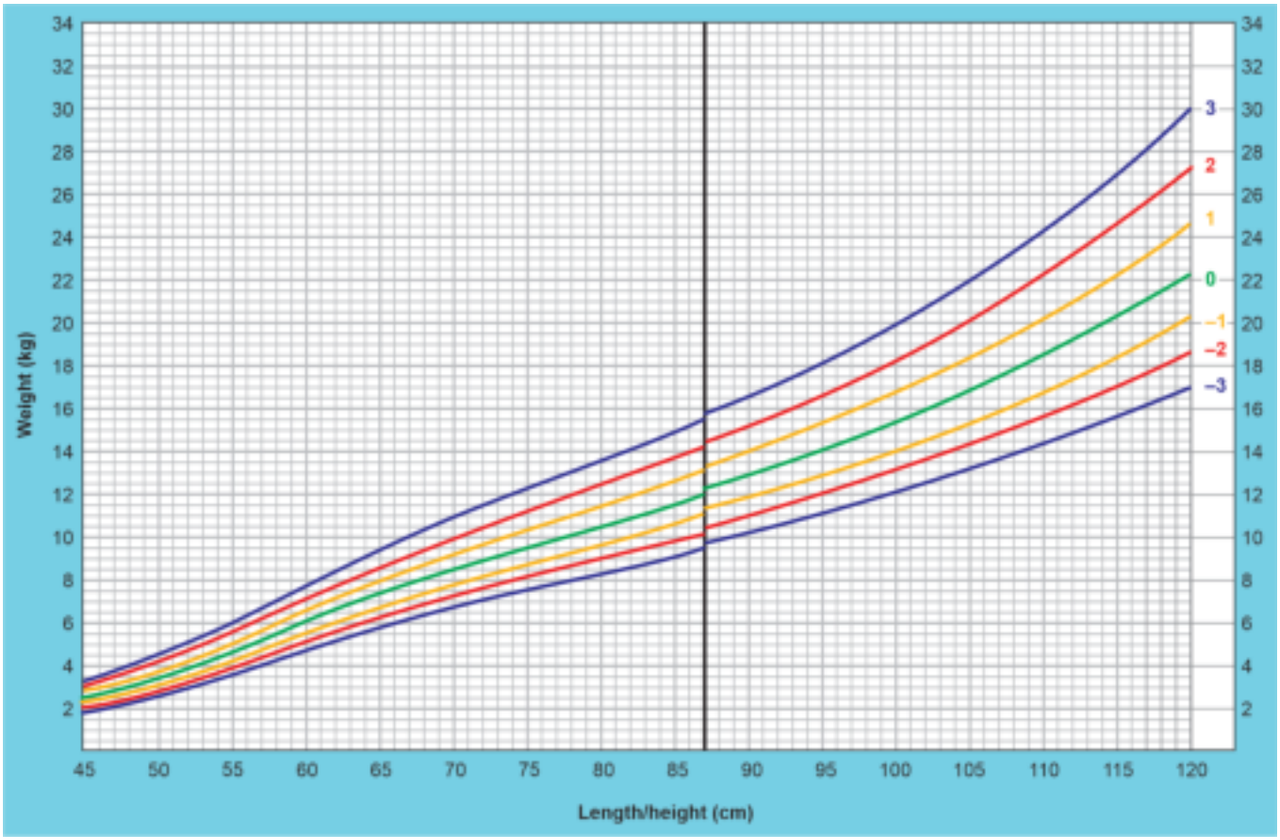
Appendix 2.2: **WHO child growth standards (Z-score): Weight-for-age: Birth to 5 years (girls)**



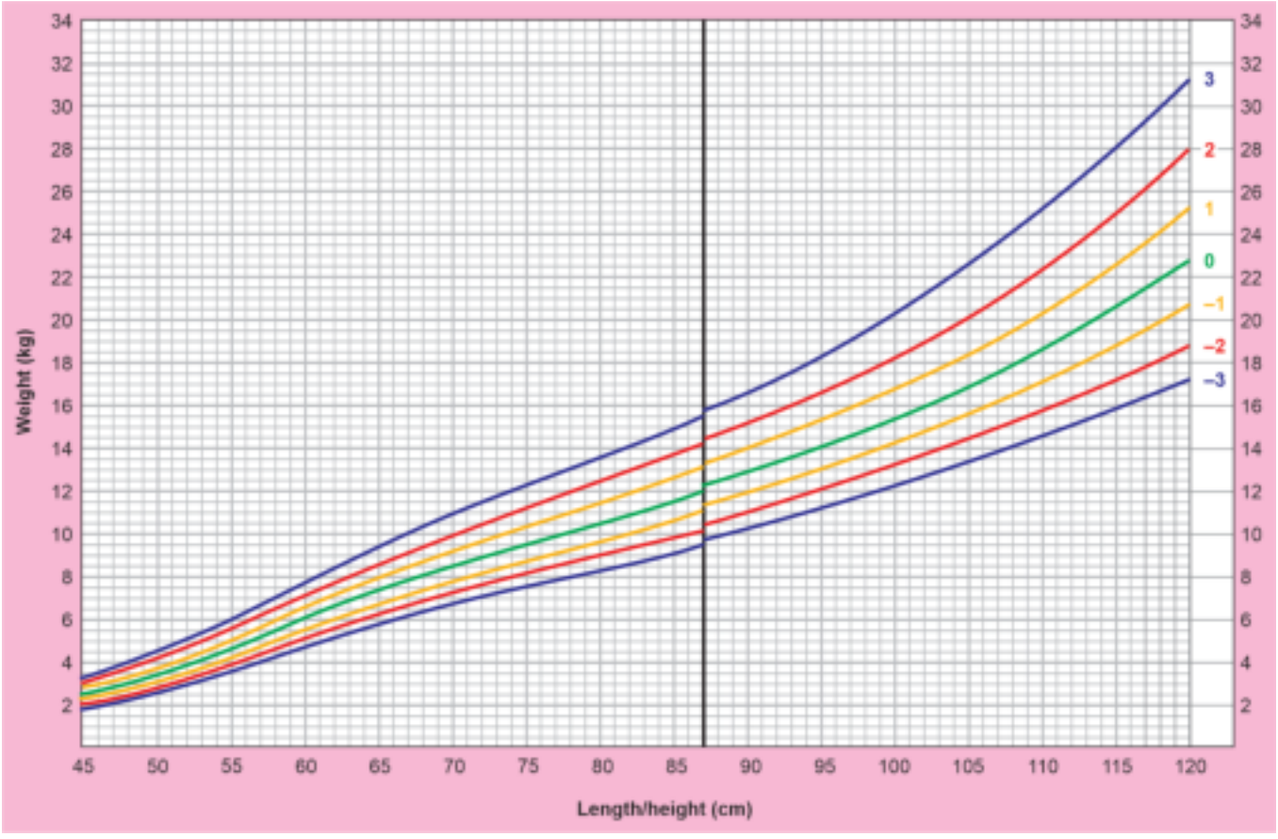
Appendix 2.3: **WHO child growth standards (Z-score): Length/Height-for-age: Birth to 5 years (boys).**



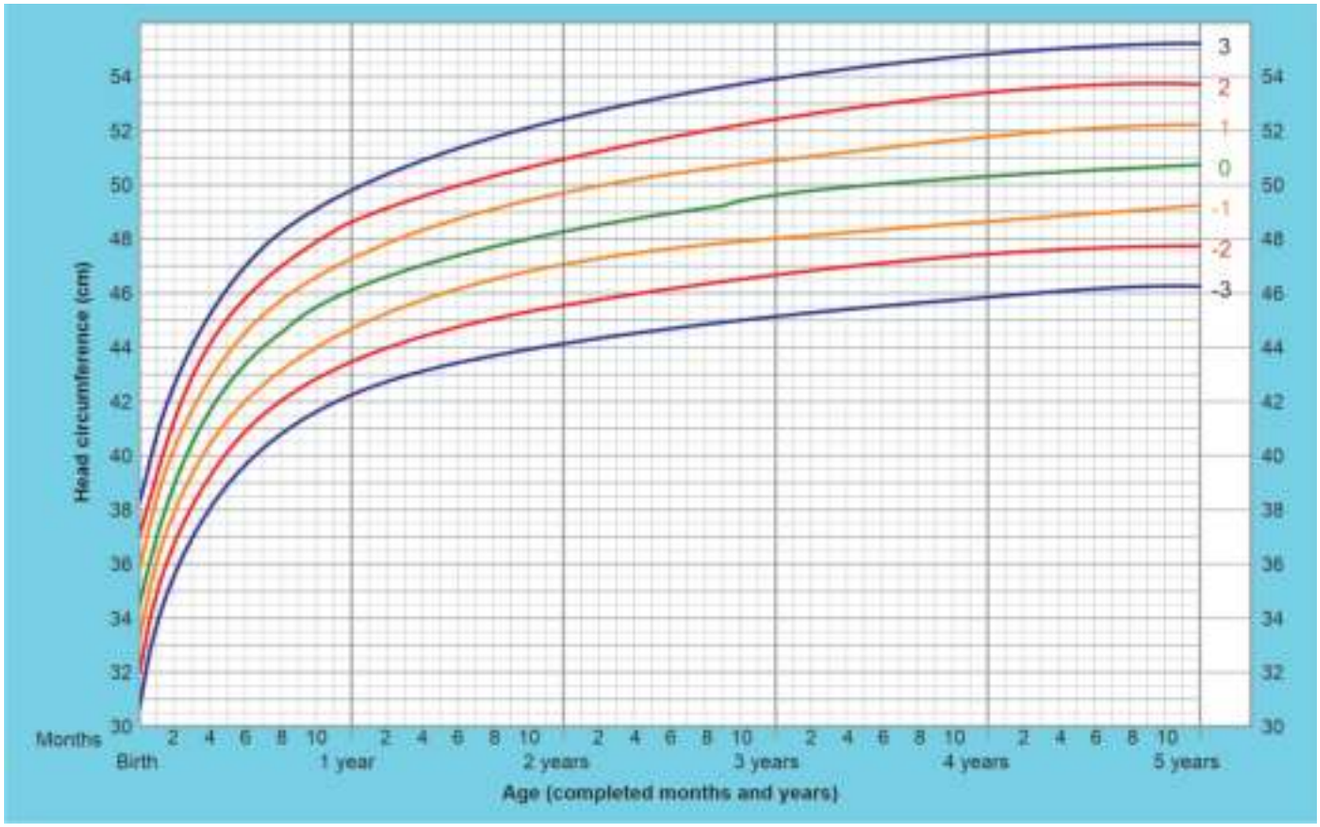
Appendix 2.4: **WHO child growth standards (Z-score): Length/Height-for-age: Birth to 5 years (girls).**



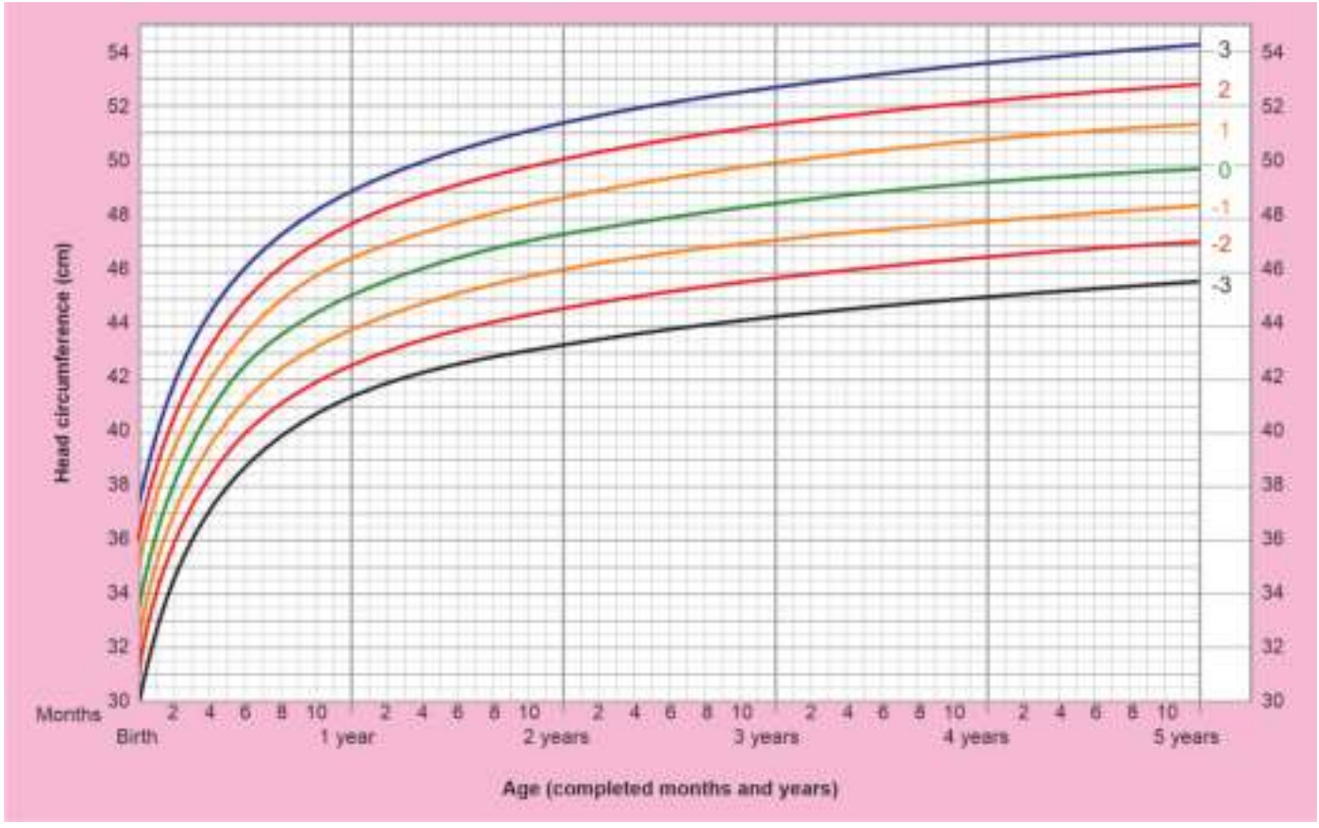
Appendix 2.5: **WHO child growth standards (Z-score): Weight-for-length/height: Birth to 5 years (boys).**



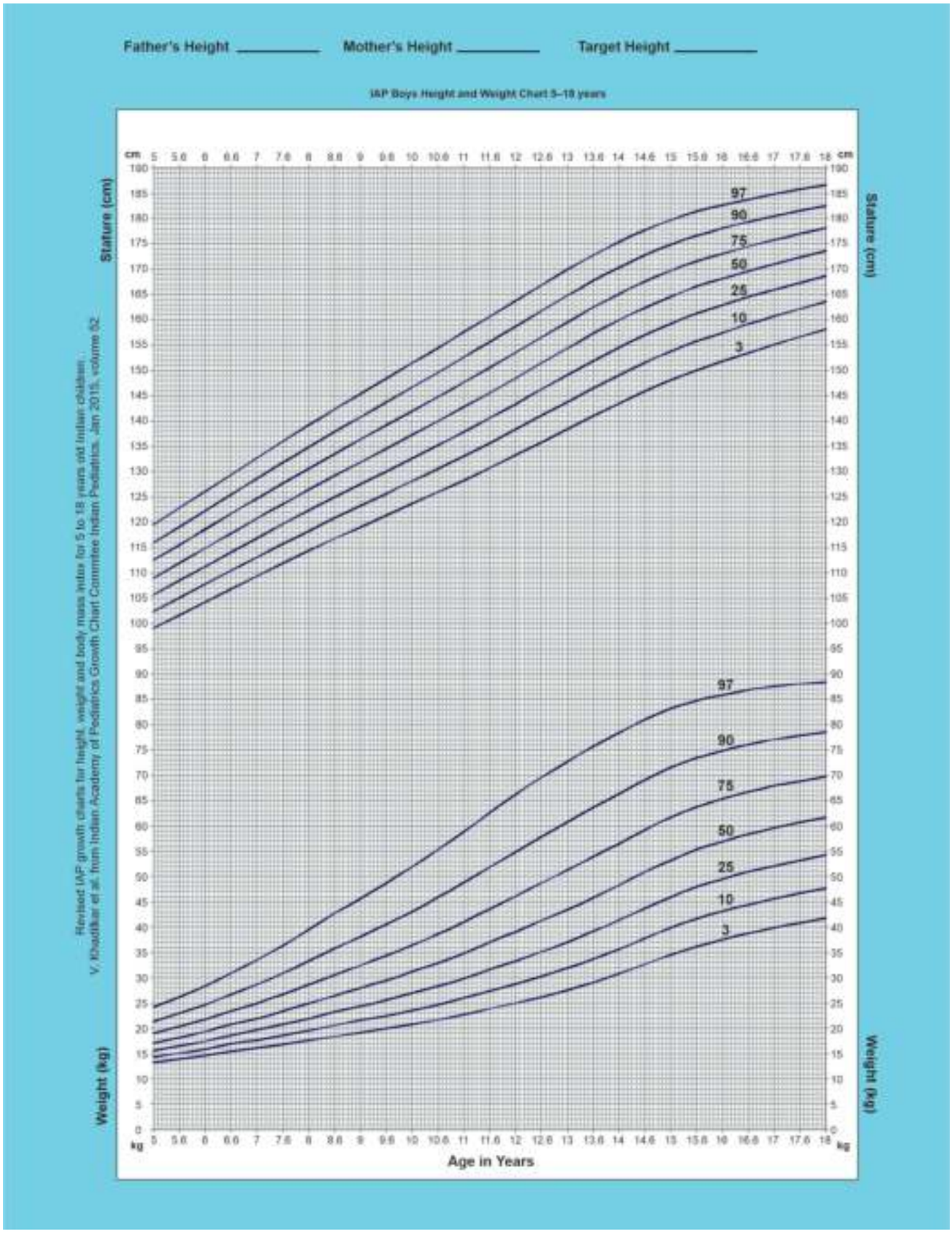
Appendix 2.6: **WHO child growth standards (Z-score): Weight-for-length/height: Birth to 5 years (girls).**



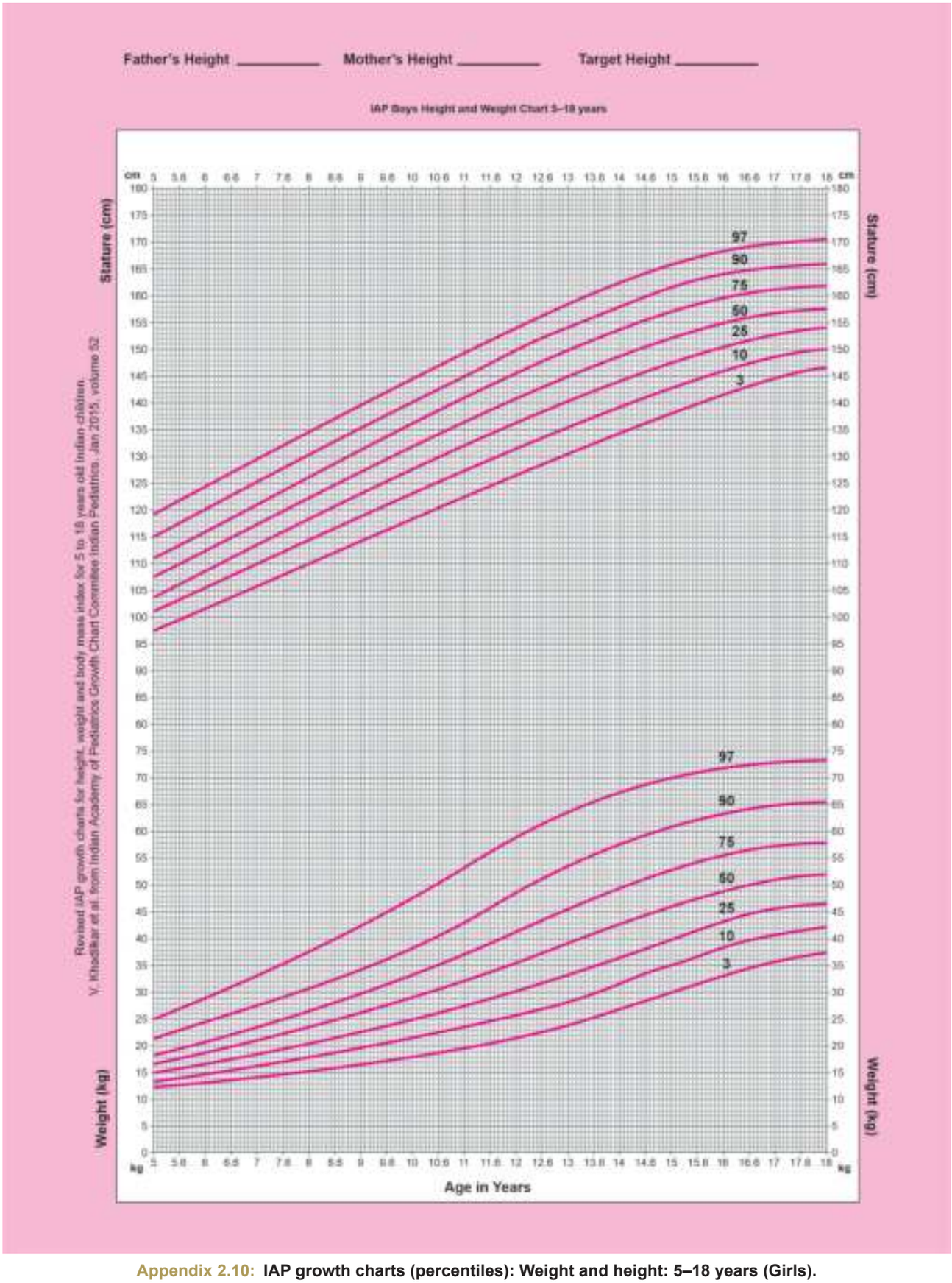
Appendix 2.7: **WHO child growth standards (Z-score): Head circumference-for-age: Birth to 5 years (Boys).**



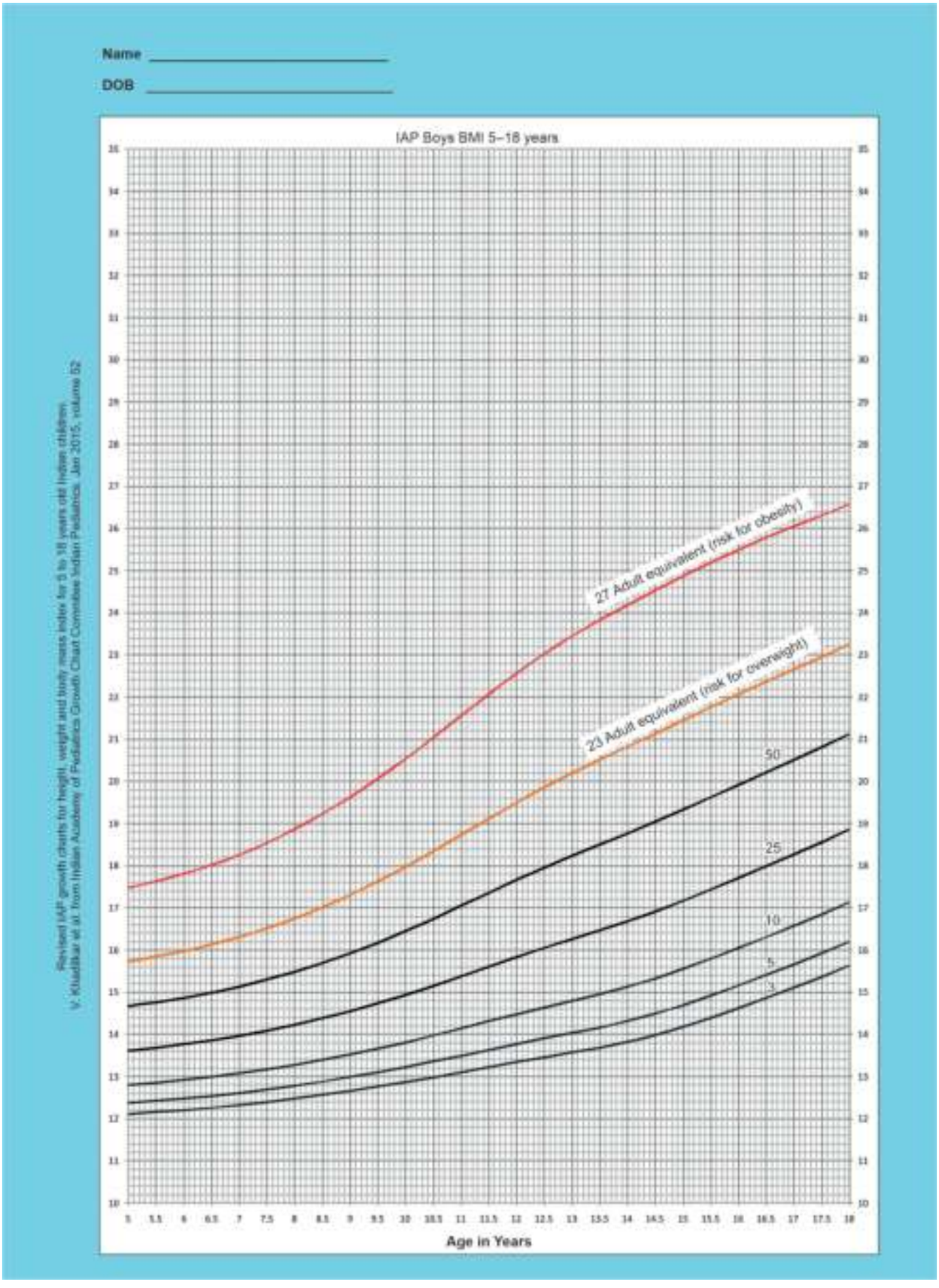
Appendix 2.8: **WHO child growth standards (Z-score): Head circumference-for-age: Birth to 5 years (Girls).**



Appendix 2.9: **IAP growth charts (percentiles): Weight and Height: 5-18 years (Boys).**



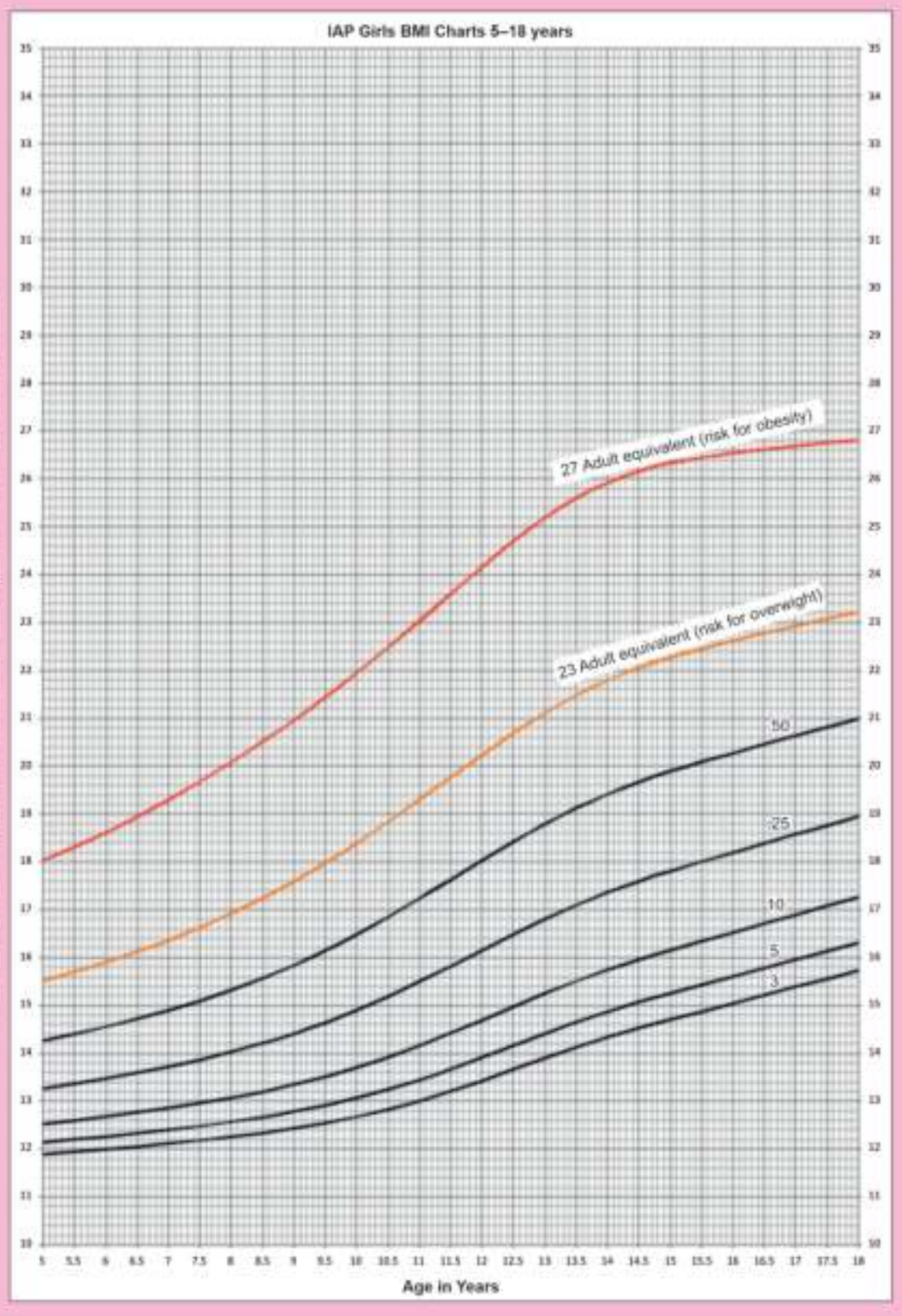
Appendix 2.10: **IAP growth charts (percentiles): Weight and height: 5–18 years (Girls).**



Appendix 2.11: **IAP growth charts: Body Mass Index (BMI): 5–18 years (boys).**

Name _____

DOB _____



Appendix 2.12: **IAP growth charts: Body Mass Index (BMI): 5–18 years (girls).**

CHAPTER 3

Growth and Development Disorders

Samir H Dalwai, Surbhi Rathi, Mukesh Agrawal

Growth and developmental problems in children are common causes of parental concerns, though all are not necessarily pathological. This chapter aims to distinguish normal variations from pathological disorders, as well as to discuss diagnostic and therapeutic approach in some common problems of growth and development.

3.1 FAILURE TO THRIVE

Failure to thrive (FTT) is a clinical state of growth failure due to any cause, characterized by any one or more of the following features:

a. Lack of growth, i.e. weight for age < 3rd percentile
b. Failure to gain weight over time on serial monitoring
c. Deceleration in growth velocity, i.e. weight dropping at least two major percentiles below the previous values over a short period, (e.g. from 75th to 25th percentile).

While *weight* is the defining criteria for FTT, other anthropometric parameters, e.g. length/height for age and body mass index, are also frequently affected and may be used for diagnosis.

Etiologically: FTT may be due to non-organic, organic or mixed causes **(Table 3.1)**.

TABLE 3.1: Causes of failure to thrive

Non-organic
a. Emotional deprivation • Maternal death/chronic illness/separation • Family disharmony • Unwanted child
b. *Nutritional:* Protein-energy malnutrition
Organic
a. *Infections:* TB, chronic malaria, kala-azar, AIDS
b. *GIT:* Cleft palate, GER, malabsorption syndrome
c. *Hepatic:* Chronic liver disease, cystic fibrosis
d. *Resp:* Recurrent infections, asthma, chronic lung disease
e. *CVS:* CCF, cyanotic CHDs, infective endocarditis
f. *CNS:* Cerebral palsy, mental retardation
g. *Renal:* Chronic UTI, renal failure, renal tubular acidosis
h. *Endocrinal:* GH deficiency, cong. adrenal hyperplasia
i. *Collagen disorders:* Rheumatoid arthritis, SLE
j. *Hematological:* Severe anemia, malignancy

GER: Gastroesophageal reflux; **GH:** Growth hormone

a. ***Non-organic FTT*** is more common (80%), usually seen in under-five children due to dietary deficiencies or emotional deprivation.
b. ***Organic FTT*** may develop at any age due to identifiable causes, e.g.
   – *Decreased food intake due to difficulties* in sucking, eating or swallowing.
   – *Impaired digestion/absorption* of nutrients, e.g. malabsorption syndromes.
   – *Increased metabolic requirements*, e.g. chronic diseases or infections.
   – *Increased losses of ingested food*, e.g. chronic diarrhea or vomiting.

Clinically these children present with:

- *Malnutrition*, e.g. growth failure, anemia, vitamin and mineral deficiencies,
- *Behavioral changes*, e.g. apathy, social withdrawal, poor eye contact/response to cuddling,
- Developmental retardation,
- Recurrent or persistent infections,
- *Signs of primary disease*, e.g. chronic infections, illnesses, emotional deprivation, etc.

Diagnostic assessment of a child with FTT may be divided into three steps: (a) preliminary clinical evaluation and investigations, (b) evaluation of response to the trial feeding and (c) revaluation with more exhaustive investigations in cases, refractory to trial feeding **(Fig. 3.1)**.

Step I. Preliminary evaluation includes:

a. *Detailed history,* specially related to dietary intake, preceding infections, e.g. diarrhea, child abuse/neglect and developmental history. Available case records, e.g. growth charts should be reviewed to confirm the presence of FF and assess the age of onset.
b. *Physical examination,* specially related to anthropometric values and signs of malnutrition, vitamin/mineral deficiencies, systemic infections/illnesses, etc.
c. *Developmental and psychosocial assessment* to search for the cause, e.g. emotional deprivation as well as consequence of FTT.

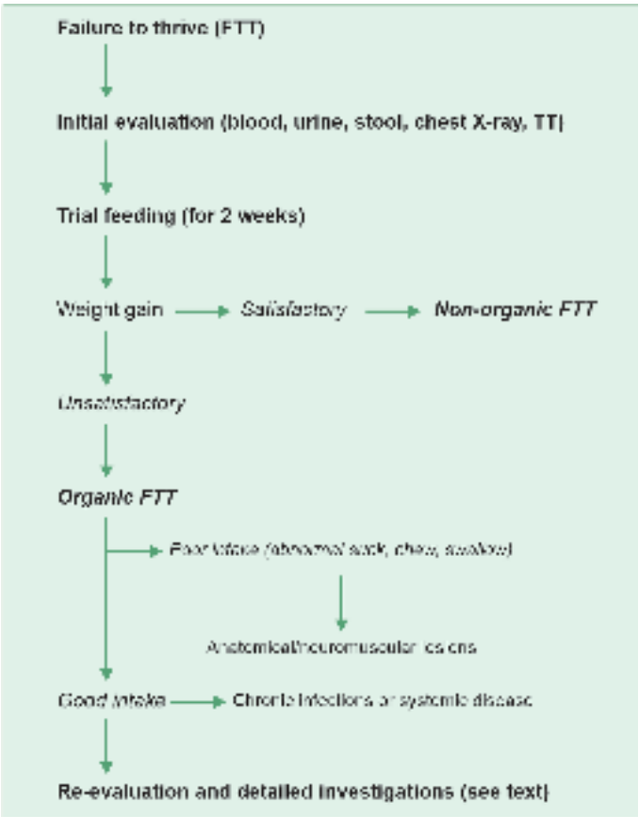


Fig. 3.1: **Diagnostic approach in failure to thrive.**

d. *Baseline investigations* to exclude common causes, i.e.
   - Complete hemogram for anemia, infections, etc.
   - Urine analysis for UTI, chronic renal disease, etc.
   - Stool analysis for malabsorption, worms, etc.
   - X-ray chest and tuberculin test for tuberculosis.
   - Skeletal survey to assess bone age.

Step II. Trial feeding: While most cases may be managed at home with nutritional counseling and periodic follow-up, hospitalization is indicated in cases with—(a) severe undernutrition with weight <60%, (b) suspected child abuse/neglect, (c) suspected organic disease, and (d) doubtful dietary intake.

In hospital, these cases should receive *trial feeding*, i.e. supervised, unlimited high caloric diet (150–200 cal/kg/day) for minimum 14 days, if necessary by nasogastric tube, along with daily weight record. A weight gain of ~50 g/day from 4–5th day onward and sustained for at least a week is considered as satisfactory, suggestive of non-organic etiology. Absence of satisfactory weight gain on trial feeding indicates organic FTT.

Step III. Re-evaluation with detailed investigations is indicated in non-responsive cases to trial feeding and includes:

- *Biochemical investigations*, e.g. blood sugar, serum proteins, liver/renal function tests, screening tests for renal tubular acidosis/aminoaciduria.
- *Endocrinal studies*, e.g. thyroid function tests, growth hormone assays including somatomedin C levels, cortisol levels, etc.
- *Genetic studies* for inborn errors of metabolism, including enzyme assays in selected cases.

In addition, all cases of FTT must.

Management of FTT aims not only to nutritional rehabilitation but also to resumption of appropriate emotional environment and treatment of the underlying organic cause. A multi-disciplinary approach is necessary in most cases, including:

a. *Nutritional management* to correct the dietary deficit and allow catch-up growth, with: (a) increasing volume, frequency and caloric density of meals, (b) avoidance of low-caloric foods and (c) dietary and micronutrient supplementation;
b. *Psychological support* and modification of home environment;
c. *Treatment of underlying cause* and associated problems, e.g. vitamin deficiencies, anemia, etc. All children should be immunized to their age-appropriate level;
d. *Parental counseling* regarding: (a) correct nutritional practices including dietary requirements, (b) use of local nutritious foods, (c) correct cooking practices, (d) maintenance of dietary hygiene, (e) inculcation of good food habits in their children, (f) myths and misconceptions about foods, and (g) Psychosocial and emotional support to the child. They should be actively involved in nutritional rehabilitation process to ensure compliance with treatment and follow-up.
e. *Periodic growth monitoring and regular follow-up* after discharge, as FTT frequently recurs due to continuance of etiological factors.

Prognosis: While initial catch-up growth is excellent in most of the adequately treated cases, it tends to slow-down over time and recurrence of FTT is not uncommon. Long-standing FTT in early life may lead to persistence of development problems, e.g. cognitive, behavioral and language disorders.

3.2 OBESITY

Body fat content changes from high adiposity state in infancy to the lowest level at 5–6 years of age, followed by gradual increase till adolescence. Obesity is a complex multi-factorial disorder characterized by an excess of adipose tissue, adversely affecting the health. While frequently used interchangeably, the terms *overweight* and *obesity* have different connotations.

Definition: *Obesity* and *overweight* in children > 2 years is defined on the basis of body mass index (BMI) as follows:

- ***Obesity:*** BMI above +3 Z-score (adult equivalent >27 kg/m^2),
- ***Overweight:*** BMI above +2 to +3 Z-score (adult equivalent >23–27 kg/m^2),

- ***Extremely obesity:*** 120% of the 95th percentile (adult equivalent ≥35 kg/m^2).

In younger children < 2 years of age, obesity is considered when the *weight for length exceeds 97th percentile.*

Prevalence: Recent years have witnessed sharp rise in prevalence of obesity among children, reported in ~5% of those above 5 years of age, increasing with age.

Etiology: Obesity results from both *hereditary* as well as *environmental* factors. It may be either *exogenous* due to life-style factors (95%) or *endogenous* due to pathological causes (5%) **(Table 3.2)**. Pathological obesity is usually central in distribution, associated with dysmorphism, growth failure and delayed bone age.

Exogenous (constitutional) obesity denotes an imbalance in dietary intake (high-fat, high-sugar, high-salt, energy-dense diet) and physical activity (sedentary life-style). Recent trends of excessive consumption of energy-dense junc foods, high screen-time and limited outdoor play have fuelled pandemic of obesity in children.

Some children are inherent prone for constitutional obesity due to genetic factors (*Polygenic obesity)* associated with single nucleotide polymorphisms of PSMA6 and PSMA3 proteosomal genes.

Endogenous (Secondary) obesity is due to pathological causes, e.g. endocrinal disorders, hypothalamic lesions and syndromic defects, e.g. Prader-Willi syndrome. *Monogenic obesity* due to loss of function mutations in leptin (LEP) and leptin receptor (LEPR) genes is more common in consanguineous families, with earlier onset < 5 years of age.

TABLE 3.2: Causes of obesity in children

A. Exogenous (95%)
- Physiological in early adolescence
- Constitutional *or* familial
- Over-eating (behavioral)
- *Poor physical activity:*
  - Habitual
  - Pathological: Physical handicaps

B. Endogenous (<5%)
- ***Endocrinal:***
  - Hypothyroidism
  - Cushing syndrome
  - Polycystic ovaries (*Stein-Leventhal syndrome*)
- ***Genetic:***
  Laurence-Moon-Biedl syndrome*
  Prader-Willi syndrome**
- ***Monogenic:*** Leptin deficiency
- ***Hypothalamic:***
  - Post-meningitic/encephalitic sequelae
  - Fröhlich syndrome***
- ***Drugs:*** Steroids, valproate, clonazepam

*Obesity, mental retardation, hypogonadism, retinitis pigmentosa
**Obesity, short stature, hypotonia, hypogonadism
***Obesity, hyperphagia, short-stature, hypogonadism, blindness

Complications: Most children with obesity are merely overweight with complications limited to psychological stress and poor body image. However, extreme obesity may be associated with significant morbidity including:

a. Skeletal: Genu valgum, slipped femoral epiphysis,
b. Respiratory: Obstructive sleep apnea syndrome,
c. Cardiovascular: Hypertension,
d. Metabolic: Hyperlipidemia, diabetes mellitus,
e. Skin: Acanthosis nigricans, striae, etc.
f. Behavioral and social problems,
g. Obesity in later life.

Pickwickian syndrome, immortalized in the Charles Dickens's novel *Pickwickian papers*, is a rare complication of extreme obesity, characterized by persistent respiratory distress with hypoxia, cyanosis, polycythemia, cardiomegaly and congestive cardiac failure.

Diagnosis of obesity *per se* requires:

a. Calculation of BMI using weight and height (weight in kg/height in cm^2);
b. Plotting of this BMI on gender-specific BMI charts **(Appendix 2.11, 2.12)** and
c. Analysis of these charts to identify the location of child's BMI on the chart. A value above the red-line indicates obesity, while values between orange and red lines indicate overweight **(Fig. 3.2)**.

While BMI remains the preferred criteria, waist circumference or waist-hip ratio may also be used to detect obesity in older children and adults. While age-wise waist-circumference charts are available for children aged 5–18 years for comparison, Waist-hip ratio is the absolute value in adults, i.e. >1.0 in males and > 0.85 in females suggesting obesity.

Assessment of a child with obesity aims to identify the cause as well presence of complications and co-morbidities, to plan appropriate management. It includes:

a. *Detailed history* to assess:
   - Dietary intake by 24-hour dietary recall, with special reference to consumption of *junk* foods, binge-eating, frequent-snacking, etc.
   - Physical activity in preceding few days including screen time;
   - Presence of family obesity, life-style and motivation;
   - Other risk factors, e.g. maternal gestation diabetes, early infant feeding, drug consumption, delayed development, etc.
b. *Physical examination* to:
   - Confirm the presence of obesity, using anthropometric assessment and BMI charts;
   - Detect markers of underlying diseases, e.g. endocrinal or genetic disorders,

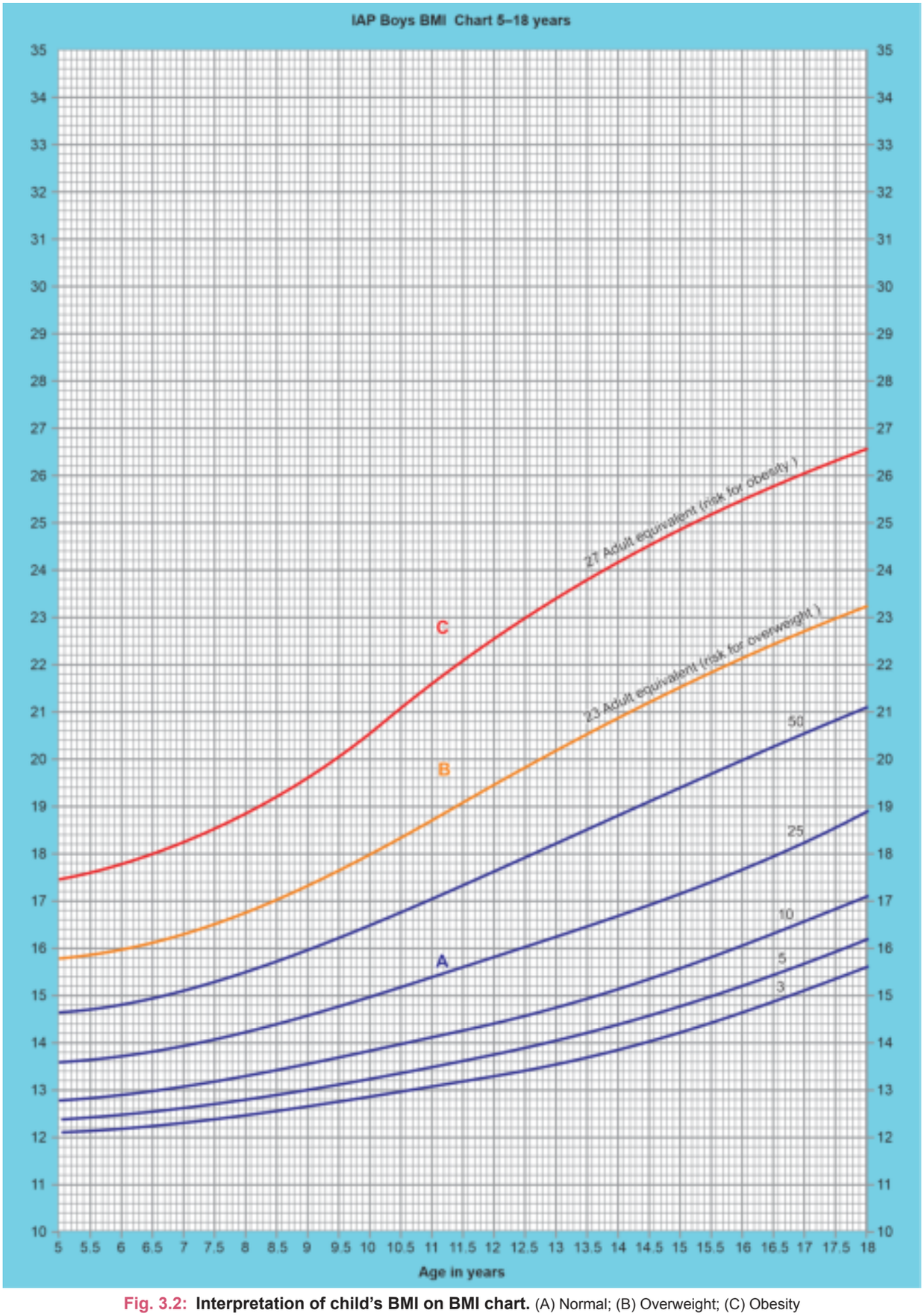


Fig. 3.2: Interpretation of child's BMI on BMI chart. (A) Normal; (B) Overweight; (C) Obesity

– Search for complications, e.g. sleep problems, hypertension, metabolic problems, etc.

c. *Psychosocial assessment* for body-image, self-esteem and secondary behavioral problems.

d. *Relevant investigations* to search for the cause of obesity as well as metabolic complications, e.g. glucose tolerance test, lipid profile, hormonal profile, etc.

Management of obesity in children should aim for gradual and sustained control with weight loss not exceeding 1.5 kg per month or >7–10% over 6 months, with a multidisciplinary approach involving pediatrician, dietician and behavioral counselor, as follows:

- ***Dietary modification,*** with low-caloric, low-fat, normal-protein, high-fiber diet, tailored to reduce the weight by ~500 g/week, is enough in most cases of overweight or mild obesity. Severe dietary restrictions and aggressive weight reduction plans are undesirable in children and may hamper normal growth. Junk foods and carbonated drinks should be avoided.
- ***Encouragement of physical activity***, e.g. outdoor games or swimming, is more acceptable to children than rigid exercise schedules.
- ***Treatment of identifiable cause.***
- ***Psychosocial support*** to the child and family.
- ***Drugs:*** General anti-obesity drugs, e.g. *orlistat* (gastric lipase inhibitor) or *sibutramine* (neurotransmitter modulator) affect growth and should be avoided in children. However, *leptin* (in leptin deficiency), o*cteotride* (in hypothalamic obesity) and *metformin* (in polycystic ovarian syndrome) may be considered in selected cases.
- ***Surgery*** like *gastric banding* or *jejuno-ileal bypass* is rarely indicated except in morbid obesity with BMI >40 kg/m^2.
- *Referral:* Children with-(a) early-onset obesity < 5 years age, (b) rapid progression, (c) delayed development, growth, and puberty, (d) neurological features and (e) abnormal metabolic workup should be referred for detailed evaluation and management under expert guidance.

Prevention: Obesity in adults usually originates in childhood and prevention should begin as early as possible with appropriate guidance and monitoring. Important preventive interventions evention of obesity in childhood include –

a. ***Dietary modifications*** to restrict high-fat, high-sugar, high-salt diet; and encourage consumption of whole grains, legumes, fruits, vegetables and nuts. JUNCS food should be avoided as per IAP guidelines **(Table 3.3)**. Fibre content in diet should be *~5 g + age in years*. Exclusive breastfeeding till 6 months followed by appropriate complementary feeding is known to curtail risk of obesity in later life.

TABLE 3.3: IAP Guidelines on consumption of JUNCS* food

- Avoid JUNCS foods or limit to one serving/ week with < 50% of total energy intake
- Limit dietary fat to <30% of total caloric intake in older children >2 years (No restriction < 2 years)
- Eliminate trans-fat from diet
- Restrict free sugar content to <5% of total energy intake
- No fruit juices/drinks below 2 years of age, and limit them to <125 ml (2–5 yrs) or <250 ml in older children with sugar content <35% w/v
- No caffeinated or carbonated drinks below 5 years of age and limit them to <100 ml/day (5–9 yrs) or <200 ml/day in older children
- Encourage seasonal fruits, vegetable, whole grains, legumes and nuts

*JUNCS: Junk food with high fat/sugar/salt content, Ultra-processed food, Nutritionally inappropriate homemade food cooked in recycled oil with high fat/salt/sugar content, Caffeinated/carbonated drinks, Sweetened sugar beverages.

Unless morbidly obese, calorie restriction is not recommended in obese children <7 years of age, rather focusing on healthy eating pattern and habits. Older children and adolescent may be advised caloric restriction to 1200–1800 cal/day, if required.

b. ***Encouragement of physical activities:*** WHO guidelines recommend average 60 minutes of moderate to vigorous physical activity, at least thrice a week in children and adolescents. Children must also be encouraged to participate in household chores. Jogging, bicycling, swimming and dancing are good calorie burners for children, apart from outdoor games (300–400 cal/hour).

c. **Limiting the screen time** as per IAP guidelines, i.e. no screen time till 2 years, less than 1 hour from 2–5 years and less than 2 hours from 5–10 years.

d. **Behavioral counseling** for parents to change their own life style as well as set realistic goals of diet and exercise in children with positive reinforcement.

e. **Periodic monitoring** to ensure success of interventional strategies and prevent recurrence of obesity.

3.3 SHORT STATURE

Short stature (SS) is a common cause of concern in school-age children, defined as the *height below the 2 Z-score or 3rd percentile for the age*. Height below the 3 Z-score indicates severe short stature.

Growth-velocity below the 10th percentile for a year indicates potential risk of SS, though many of these children in pre-pubertal age group are merely *slow-growers.*

Prevalence: While 35.5% of under-five children are stunted due to nutritional causes, ~3% of school children are estimated to be short-statured in India as per above mentioned criteria.

Types: According to the growth potential and patterns of growth, SS may be broadly classified into three types:

a. ***Normal variant SS*** (20%), i.e. children with normal growth potential, who are relatively slow grower in childhood but achieve normal adult height by more marked growth spurt during adolescence or delayed completion of puberty.
b. ***Primordial SS*** (15–20%), i.e. children with inherently low growth potential, who remain short-statured even after completion of puberty.
c. ***Secondary SS*** (50–60%), i.e. children with normal growth potential, which is hampered by exogenous factors, e.g. diseases.

Etiology: Important causes of SS are listed in **Table 3.4**, though characteristics of some common types are as follows:

- ***Familial SS*** is common in India, due to short-statured parents. These children are normal at birth but their growth velocity declines during pre-school age-group. Subsequently, they resume normal growth velocity by mid-childhood but without catch-up growth. As the onset and completion of puberty occur at normal age, ultimate adult height is short but comparable to their parents **(Fig. 3.3A)**.
- ***Constitutional SS*** is similar to familial SS, but with two differences-parents have normal height and puberty is usually delayed to enable them to grow for a longer period and attain near-normal adult height **(Fig. 3.3B)**.
- ***Primary SS*** denotes inherently low growth potential due to genetic disorders, e.g. skeletal dysplasia or intrauterine growth retardation. These children are usually low birth weight, have lower growth velocity (<4 cm/year) in childhood and remain short-statured in adulthood. Children with skeletal dysplasia also have distorted body proportions.
- ***Secondary SS*** is the commonest cause of preventable SS, in which growth velocity is hampered by prolonged illnesses, e.g. malnutrition, infections or systemic diseases during early childhood. Delayed bone age is a consistent feature in these cases, which may or may not correspond to height age. Growth hormone deficiency is an important cause of SS due to hypopituitarism, reduced somatomedian levels or receptor insensitivity, i.e. *Laron syndrome.*

Important differentiating features between common causes of short stature are shown in **Table 3.5**.

Diagnostic assessment: All short-statured children are not necessarily abnormal and a preliminary clinical evaluation with baseline investigations, periodic height monitoring and parental reassurance is enough in most pre-pubertal children with borderline SS.

Detailed evaluation and referral to specialized services is indicated in children with:

TABLE 3.4: Common causes of short stature

A. Normal variants short stature
- Familial
- Constitutional

B. Primary short stature (primordial dwarfism)
- Intrauterine growth retardation (IUGR)
- *Genetic:*
  - *Chromosomal:* Mongolism, Turner syndrome
  - *Inborn errors of metabolism:* Hurler syndrome
  - *Others:* Progeria, Silver-Russell syndrome
- *Skeletal dysplasia*
  - *Short-limb:* Achondroplasia
  - *Short-trunk:* Spondylo-epiphyseal dysplasias

C. Secondary short stature
- *Nutritional:* PEM, zinc deficiency
- *Emotional:* Psychosocial dwarfism
- *Chronic infections:* TB, AIDS, UTI, worms
- *Chronic systemic diseases:*
  - *GIT:* Malabsorption syndrome, chronic liver disease
  - *Renal:* Chronic renal failure, renal tubular acidosis
  - *Cardiac:* Cyanotic CHDs, recurrent CCF
  - *Pulmonary:* Asthma, tuberculosis
  - *CNS:* Diencephalic syndrome of infancy
  - *Blood:* Hemoglobinopathies, malignancies
- *Endocrinal disorders:*
  - Growth hormone deficiency
  - Hypothyroidism
  - Cong. adrenal hyperplasia, Cushing syndrome
- *Iatrogenic:* Steroids, cytotoxics, radiotherapy

a. Severe short stature with height <-3 Z-score,
b. Short stature with height <-2 Z-score, after adjusting MPH,
c. Downward crossing of height by two major percentiles in 6 months,
d. Pre-pubertal height velocity < 5 cm/year,
e. Disproportionate SS at any age,
f. Clinical features suggestive of genetic or secondary cause,
g. Persistent SS after the onset of puberty,

Important steps in evaluation of these children include **(Fig. 3.4)**:

Step I. Confirm the presence of SS by recording the patient's height and comparing it with reference norms. Previous personal growth charts, if available, should be reviewed for growth velocity in the past and assess the timing of the growth faltering.

In borderline cases, height velocity should be measured for next 12 months before further workup. A height velocity of <5 cm in pre-pubertal years is significant and needs further evaluation.

Step II. Exclude normal variant SS by–(a) review of previous height records and (b) evaluation of parent/

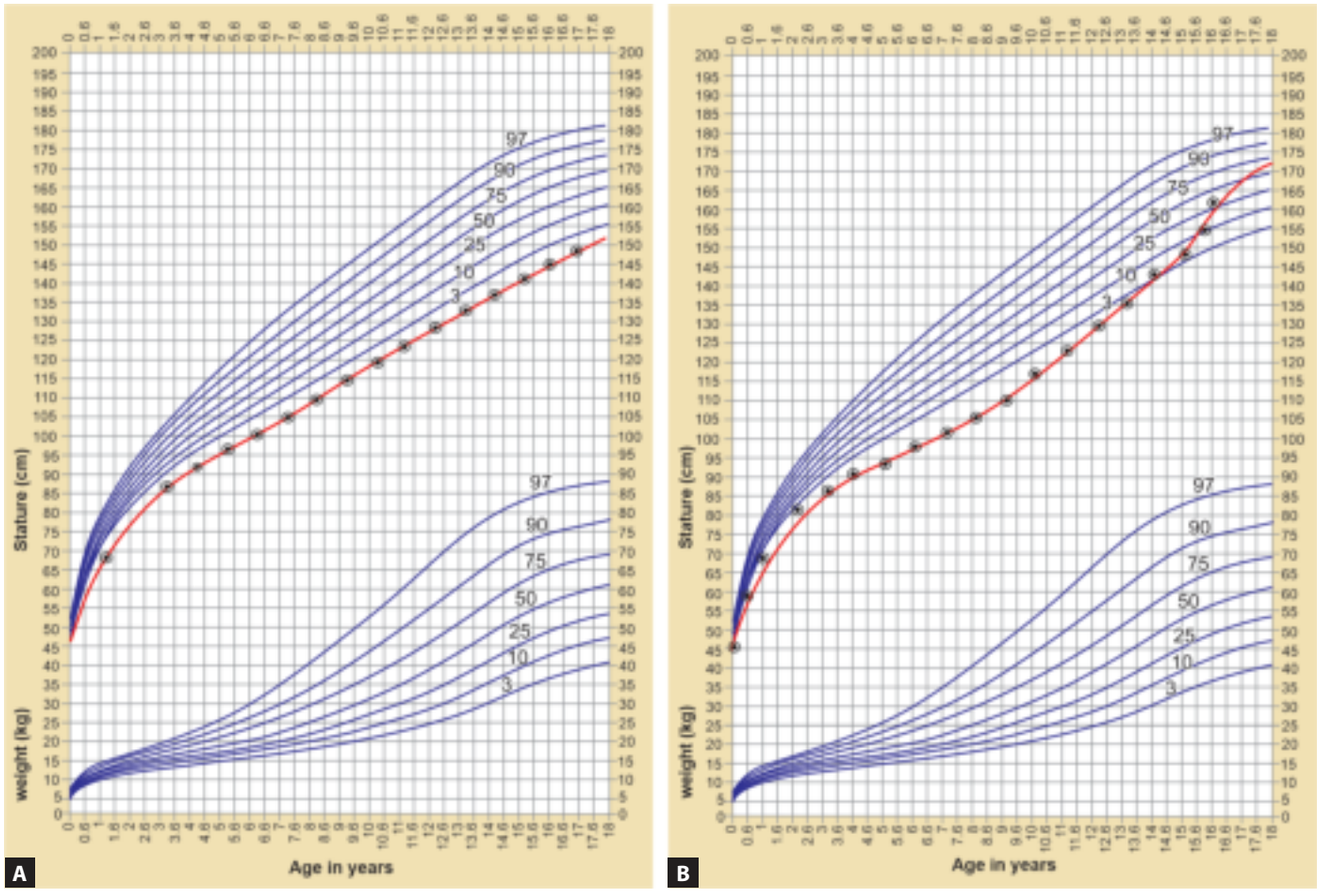


Fig. 3.3A and B: **(A) Familial SS.** Normal at birth > low growth velocity <3rd percentile throughout childhood and adolescence > normal age of onset of puberty > Low final Height, comparable to mid-parental height; **(B) Constitutional SS.** Normal at birth > low growth velocity in early childhood > late onset of puberty with pick-up (accelerated) growth > normal final height.

TABLE 3.5: Differential diagnosis of short stature

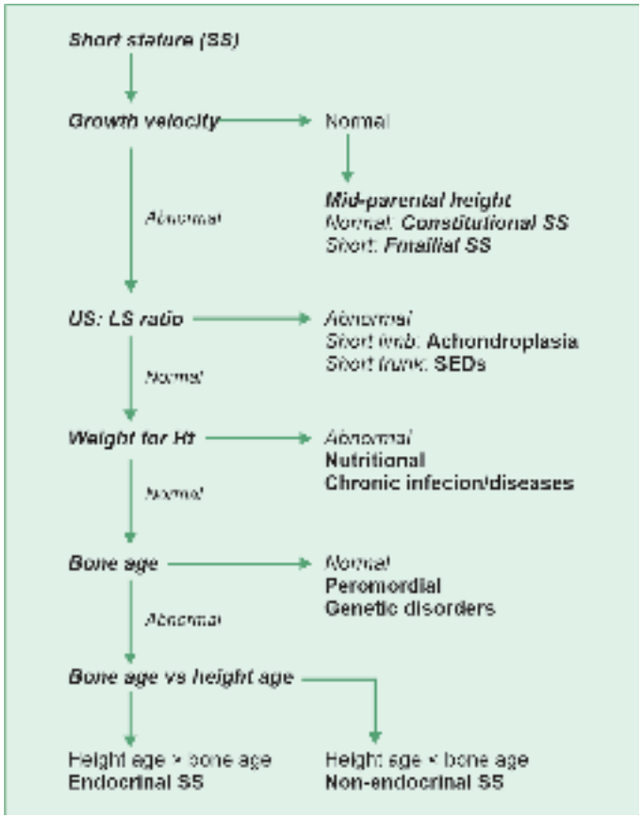
	Familial	*Constitutional*	*Genetic*	*Skeletal*	*Secondary*	*Endocrinal*
Parental height	Less	N	N	N	N	N
Birth weight	N	N	Less	N	N	N
Early GV (<3 years)	Less	Less	Less	Less	N/Less	N/Less
Late GV (>3 years)	N	N	Less	Less	Less	N/Less
Onset of puberty	N	Late	N/Late	N	N/Late	L/E
Final adult height	Less	N	Less	Less	N/Less	Less
Body proportions	N	N	N	Disproportionate	N	N
Weight for height	N	N	N	More	Less	More
Bone age vs CA	N	N	N	N	Less	Less
Bone age vs HA	More	N	More	More	More	Less

Note: Salient features are given in bold and italics, **GV:** Growth velocity, **CA:** Chronological age, **HA:** Height age.

sibling height. Adult height in familial cases may be predicted within reasonable limits (± 6.5 cm) by using standard graphs or following formula:

- Boys = {(Mother's height +13) + Father's height}/2
- Girls = {(Father's height – 13) + Mother's height}/2

Adult height may also be predicted by plotting the mid-parental height on MPH percentile growth chart. The percentile line nearest to this point is mid-parental 50th percentile and child's own percentile curve is expected to be between 10th and 90th percentile on this chart.



SED: Spondyloepiphyseal dysplasia

Fig. 3.4: Diagnostic approach to short stature.

Step III. Differentiate between proportionate and disproportionate SS by recording *upper segment: Lower segment ratio* and *arm-span*. Disproportionate SS is most obvious in skeletal dysplasia, e.g. achondroplasia (short-limb), spondyloepiphyseal dysplasia (short-trunk) and hypothyroidism (short-limb).

Step IV. Evaluate the bone age by age-appropriate skeletal X-rays and compare it with chronological as well as height age. Bone age is less than the height age in endocrinal disorders, e.g. hypothyroidism. (Height age is the age at which his/her current height would match 50th percentile curve on growth chart).

Step V. Exclude organic causes, e.g. malnutrition, chronic infection or diseases and emotional deprivation by detailed history and clinical evaluation, specially related to birth weight, dietary intake, previous illnesses and inter-family relationship.

Step VI. Relevant investigations, including:

a. *Baseline investigations in all cases*
   - Routine blood, urine and stool analysis
   - X-ray chest and tuberculin test to exclude tuberculosis
   - Skeletal survey for bone age and dysplasia

b. Selected investigations, depending on clinical suspicion
   - Chromosomal analysis (karyotyping)
   - Biochemical tests for diabetes and liver/renal functions
   - Endocrinal work-up, e.g. thyroid function tests, growth hormone assays, etc.
   - Serological tests for celiac disease.

Management of SS depends on the cause and includes:

- Adequate nutrition with high protein and caloric diet and micronutrient supplements.
- Treatment of underlying infections and infestations
- Specific treatment for identified cause, e.g. thyroxine for hypothyroidism, gluten-free diet for celiac disease, etc.
- Follow-up with periodic height monitoring till the final height is achieved.
- Growth hormone therapy, as discussed below.

Growth hormone (GH) therapy is used not only in growth hormone deficiency (Ch 22.2.2) but also in many other causes of SS, e.g. chronic renal disease, Turner/Noonan syndrome, intrauterine growth retardation and Idiopathic SS, etc. It should be started as soon as possible after confirmation of diagnosis, using a recombinant GH preparation as daily night injections (25–50 µg/kg, subcutaneously). Higher doses may be used during puberty. Maximum response is seen during first year of therapy which must be continued till height velocity drops <2.5 cm/yr or bone age reaches >14 years in girls and >16 years in boys.

Pseudotumor cerebri is a significant but rare complication of GH therapy. Rare side-effects include fluid retention, impaired glucose tolerance, worsening of scoliosis and slipped capital femoral epiphysis. Very rarely, there is increased risk of malignancy in some predisposed genetic conditions.

3.4 TALL STATURE

Tall stature, defined as *height >97th percentile for the corresponding age* is relatively uncommon.

Some children may appear taller than others in early childhood due to individual variations and ectomorphic body build. Hildren with precocious puberty are relatively taller in early puberty than others, though final adult height in them is normal due to early skeletal maturation and completion of puberty.

Etiology: Most of these cases are *normal variants* due to familial or constitutional features, though pathological tall stature indicates chromosomal, genetic or endocrinal etiology **(Table 3.6)**. Some unique causes of tall stature, not discussed elsewhere, are as follows:

Marfan syndrome is the commonest cause of pathological tall stature in children. It is an autosomal dominant connective tissue disorder, with abnormal synthesis of *fibrillin-1*, an α-glycoprotein in elastin fibers.

TABLE 3.6: Causes of tall stature

- **Familial** (tall parents)
- **Constitutional**
- **Genetic**
  - *Chromosomal:* Klinefelter or XXY syndrome
  - *Genetic:* Marfan syndrome, homocystinuria
- **Endocrinal**
  - Hyperpituitarism (pituitary gigantism)
  - Precocious puberty
  - *Others:* Thyrotoxicosis, Beckwith syndrome
- **Cerebral** gigantism *(Soto's syndrome)*

Clinically, these cases are characterized by tall stature, increased arm span (US:LS ratio), arachnodactyly (long fingers), ocular abnormalities, (e.g. lens dislocation, iridodonesis) and cardiac abnormalities, (e.g. mitral valve prolapse, aortic regurgitation).

Cerebral gigantism (Soto's syndrome) is a rare hypothalamic disorder, characterized by rapid linear growth during first 3–4 years of age, macrocrania, mental retardation, gait abnormalities and normal or precocious puberty. It may be differentiated from pituitary gigantism by normal growth hormone levels and delayed skeletal maturation as compared to height.

Diagnostic evaluation of tall stature aims to differentiate normal variants form rare pathological causes, usually based on positive family history (correlate with mid-parental height) and normal physical examination. A suspected cases of pathological tall stature needs complete clinical evaluation, including ophthalmic and cardiac assessment (for Marfan syndrome and homocystinuria) and detailed investigations, including:

a. Radiological determination of bone age.
b. Karyotyping to exclude chromosomal disorders, e.g. Klinefelter syndrome.
c. Hormonal studies, e.g. growth hormone assays and thyroid function tests.

Treatment: No treatment is usually necessary for tall stature *per se*, except the treatment of underlying cause. Hormonal therapy with sex-steroids to accelerate epiphyseal fusion and early completion of puberty is occasionally used in children with severe tall stature (with predicted adult height >3 SD) and significant psychological stress.

3.5 DEVELOPMENTAL DELAY

Developmental status of a child is usually measured and expressed either as *Developmental age*, i.e. the age for which expected milestones have been achieved or as *developmental quotient* (DQ) derived by dividing developmental age (DA) by chronological age (CA) and multiplied by 100 (DQ = DA/CA×100). DQ is an absolute value and not a percentage.

Developmental delay (DD) refers to the significant delay in achieving developmental milestones in any one or more of the following domains: (a) gross and fine motor, (b) social-personal, (c) cognition, (d) speech and language, and (e) activities of daily living, as compared to peers, i.e. *a performance of less than 2 SD for the age-appropriate norms. A DQ of less than 70 is also considered as developmental delay*.

This term is reserved only for children below 5 years of age, in whom formal intelligence quotient (IQ) testing is not possible. The term *'Intellectual disability'* is used in older children (Ch 3.6).

Types: Developmental delay may be further classified as:

a. ***Global developmental delay*** (GDD), when two or more domains are affected, and
b. ***Development dissociation***, when the delay is limited to only one domain or is disproportionately more in one domain as compared to others. DA or DQ should always be measured in different domains separately, to identify developmental dissociation, if any.

Developmental deviance, i.e. differences in the sequence of achieving different milestones in one or more domain may be innocent or sinister, e.g. some infants may not creep before they start walking and should not be construed as abnormal.

Developmental regression, refers to the loss of previously acquired milestones, usually suggestive of a neurodegenerative disorder.

Etiology of DD is identifiable only in ~70% cases and common causes include genetic disorders, intrauterine infections, e.g. congenital rubella syndrome, perinatal hypoxia at the time of birth and postnatal insults to developing brain till 2 years of life. Emotional deprivation may also lead to DD, specially in social domain while hearing impairment is the commonest cause of delay in language development **(Table 3.7)**.

Diagnostic approach for a child with suspected DD aims to-(a) confirm the presence of DD *vis a vis* individual variations and deviance, (b) differentiate global DD from developmental dissociation, deviance or regression, (c) identify the cause of DD, if possible, and (d) search for presence of co-morbidities, if any.

Early detection of developmental delay involves a step-wise approach:

a. *Informal developmental surveillance* of all children during all health-care visits;
b. *Formal development screening* of all children at scheduled intervals;
c. *Formal developmental assessment* of children with abnormal screening results.

Step I. Informal developmental surveillance, discussed earlier (Ch 2.7) is a continuous and informal process

TABLE 3.7: Causes of developmental delay

- **Idiopathic (30%)**
- **Familial**
- **Genetic disorders:**
  - *Chromosomal:* Down syndrome, Fragile X syndrome
  - Inborn errors of metabolism: Phenylketonuria
  - Mitochondrial disorders
- **Fetal brain injury:**
  - Congenital brain malformations
  - Intrauterine infections, e.g. CRS
  - *Teratogens:* Alcohol, phenytoin
  - Obstetric complications
- **Perinatal brain injury:**
  - Prematurity and/or low birth weight
  - Birth asphyxia and birth injuries
  - *Metabolic:* Hypoglycemia, kernicterus
- **Postnatal brain injury** (in first 2 years):
  - *Infections:* Meningitis, encephalitis
  - Head injury
  - *Endocrinal:* Hypothyroidism
  - *Prolonged hypoxia:* Seizures, ALTS
  - *Toxic:* Lead poisoning
  - *Metabolic:* Hypoglycemia
- **Environmental:**
  - Emotional deprivation
  - Visual/hearing disability

ALTS: Acute life threatening events

to assess the development of a child during regular health check-up/immunization visits by asking the developmental history from mother, observing his/her behavior in the clinic and examination to elicit common age-appropriate milestones. *A developmental delay* may exist when the child fails to achieve developmental milestones at the expected age, despite adjustments for individual variations. However, the purpose of this surveillance is not to draw a line between normal and abnormal, but to identify high-risk children, who need referral for formal assessment.

Mother and child protection (MCP) card also includes a check-list of red-flag signs for delayed development for different ages, which can also be used by field health workers to identify a high-risk child, who need referral for further assessment **(Table 2.12)**.

Step II. Formal developmental screening involves use of validated and locally appropriate screening tools to identify high-risk children who needs detailed developmental assessment.

IAP recommends that—

a. All children should be screened by these screening tools at the age of 9–12 months, 18–24 months and at school entry, coinciding with immunization visits, and
b. High-risk children should also be additionally screened at 4–6 months.

Many screening tests are available for this purpose, including widely used Denver developmental screening test (DDST), or locally developed *Phatak's Baroda development screening test* or *Trivandrum development screening test*, discussed in Ch 2.7.

TABLE 3.8: Referral criteria for formal developmental assessment

- Delayed development on informal surveillance
- Delayed development on formal screening
- Family h/o delayed development/intellectual disability
- Neuromuscular or neuroregression disorders
- Presence of dysmorphic features/physical stigmata **(Table 3.9)**
- Presence of vision or hearing disabilities
- Abnormal neuroimaging findings

DD: Developmental delay, **ID:** Intellectual disability

However, these screening tests should not be used to assign development quotient/intelligence quotient or to declare the developmental delay *but only* to identify high-risk children for formal assessment.

Step III: Formal development assessment tests: Developmental delay is a shattering diagnosis for parents and should not be made without formal assessment. **Table 3.8** enlists high-risk children for developmental delay, who must be referred for formal developmental assessment, including those identified on informal surveillance or screening tests.

Formal developmental assessment tests must be administered only by trained personals, usually developmental pediatricians or clinical psychologists. Many such tests are available and the choice depends on the age of the child, expected area of developmental abnormality and familiarity of the assessor with the test.

Bayley scale of infant development (BSID-IV) for children aged 16 months to 42 months and its Indian version-*developmental assessment scale of Indian infants* (DASII) for children aged 0–30 months, are commonly used in India to confirm the presence and severity of developmental delay in young children.

Other domain-specific tests are also available, e.g. Vineland adaptive behavior scale II for personal-social domain and clinical linguistic/auditory milestone scale (CLAMS) for language skills.

Step IV. Assessment of a child with confirmed DD on formal developmental assessment tests needs a detailed history, clinical examination, relevant investigations and developmental evaluations to arrive at an etiological diagnosis, to identify the line of further management, predict the expected outcome and parental counselling. Important components of this assessment include—

a. *Detailed history,* with special reference to similar family history (pedigree analysis), consanguinity, adverse antenatal or perinatal events and behavioural problems, e.g. attention-deficit.
b. *Review of the development record* to distinguish between– (a) delay from birth or later, (b) global developmental

delay from developmental dissociation, (c) developmental delay and developmental regression, and (d) non-progressive delay and progressive worsening.

Presence of developmental dissociation (selective delay in one or two domains) narrows the diagnostic possibilities, e.g. hearing impairment for speech/language domain, vision/hearing impairment for personal-social domain, neuromuscular disorders for motor domain, etc. Similarly, a non-progressive global delay indicates cerebral palsy, whereas a deviancy or regression in social and communication domains may indicate autism spectrum disorder.

c. *Physical examination* with special reference to anthropometry, physical stigmata **(Table 3.9)**, vision/hearing problems and neurological signs. Ophthalmoscopic examination is highly informative in etiological diagnosis of developmental delay, e.g. presence of chorioretinitis in intrauterine infections, cherry-red spot in neurodegenerative disorders, papilledema in hydrocephalus, etc.
d. *Relevant investigations,* depending on suspected etiology, mainly include cytogenetic, biochemical and neuroimaging tests **(Table 3.10)**.
e. *Family screening:* Once a genetic diagnosis is firmly established in the index case, parents and siblings should be screened for assessing the risk of recurrence and genetic counselling.

Management: Except for few causes, e.g. hypothyroidism, phenylketonuria and lead intoxication, majority of the disorders with developmental delay have no pharmacological cure and management *primarily aims to achieve maximum functional independence and eliminate function-limiting factors*, e.g. vision/hearing impairment or seizures.

Management and rehabilitation program of each child needs to be individualized, according to their needs and potential. A multidisciplinary team approach is essential in these cases, involving following interventions:

a. Physiotherapy and occupational therapy for neuromuscular dysfunctions.
b. Management of associated deficits, e.g. hearing, vision and speech delay, seizures, etc.
c. Psychotherapy or behavioral modification.
d. Schooling, preferably in a regular school, as far as possible.
e. Parental support and counselling

Parental counselling is an essential component of the management of development delay to help them understand the:

a. cause of developmental delay.
b. goals of diagnostic and therapeutic interventions,
c. anticipatory course and expected long-term outcome,
d. strengths of the child, and
e. potential to prevent recurrence in subsequent children.

Managing a child with developmental delay is often a frustrating task for parents, who should be counselled in clear and compassionate manner but without kindling unrealistic expectations.

TABLE 3.9: Common physical stigmata in developmental delay

- *Size :* Tall/short stature, obesity, failure to thrive
- *Head :* Microcephaly, hydrocephalus
- *Eyes :* Slanting eyes, microphthalmia, cataract
- *Ears :* Deformed or low-set ears
- *Face :* Coarse facies, retro-/prognathia
- *Mouth :* Cleft lip/palate, macroglossia
- *Hair :* Sparse, kinky, light-colored
- *Neck :* Short or webbed neck
- *Limb :* Brachy-/arachnodactyly, poly-/syndactyly
- *Skin :* Café-au-lait spots, adenoma sebaceum
- *Genitals :* Hypogonadism, hypospadias

TABLE 3.10: Investigations in developmental delay

- *Neuroimaging:* CT/MRI for structural CNS lesions
- *Electrophysiological studies:* EEG, EMG, BERA
- Serological tests for intrauterine infections
- Hormonal assays, e.g. thyroid function tests
- *Toxin screening:* Lead, uric acid
- *Cytogenetics:* Karyotyping, Chromosomal microarray, WES
- *Urinalysis for IEM:* Ferric chloride test, AA chromatography
- Enzyme assays for neurodegenerative disorders

WES: Whole exome sequencing; **AA:** Amino acid

Child Development Units (CDUs)

Child development units have been established in many large hospitals and child-health centers for early diagnosis and comprehensive management of developmental delay. These units are served by a multi-disciplinary team of pediatricians, developmental pediatricians, neurologists, psychologists, physiotherapists, occupational therapists, speech therapists and special educators.

These units not only offer diagnostic and therapeutic services for developmental delay or intellectual disability but also provide management of co-morbidities, behavioral interventions, special educational activities, and parental counselling.

3.6 INTELLECTUAL DISABILITY

Intellectual disability (ID) is defined under DSM-V criteria as follows:

1. *Deficit in intellectual functions,* e.g. reasoning, problem-solving, abstract thinking, academic learning, etc., with measured IQ score of <70 (or <-2SD for same age and culture) *(IQ = Mental age/Chronological age × 100).*
2. *Deficit in adaptive functions* needed to live in an independent and responsible manner, e.g. communication, social/interpersonal skills, self-care or

TABLE 3.11: Severity grading of intellectual disability

Severity	*Level support*
Intermittent (Mild, IQ 52–60)	No constant support needed
Limited (Moderate, IQ 36–51)	Requires occupational support, has independent home life
Extensive (Severe, IQ 20–35)	Requires occupational support as well as support for daily activity
Pervasive (Profound, IQ < 20)	Institutionalized care is often necessary

independence at home or community settings, e.g. shopping and school/work functioning.

3. Onset of these deficits or limitations during developmental phase <18 years of age.

The term ID should be used only in children above 5 years of age who meet all of the above criteria and in whom formal intelligence quotient (IQ) testing is possible.

Classification: Conventional classification of ID based on IQ scores has been largely replaced by the revised classification systems based on the need for support system necessary for daily functioning **(Table 3.11)**.

Incidence: It is estimated that ~3% of general population fulfills the diagnostic criteria for ID, though >80% of them have only mild deficits. ID is more common in males and in children with *risk factors, e.g.* similar family history, consanguinity and perinatal complications.

Etiology of ID is similar to that of developmental delay **(Table 3.7)**. It may be genetic, environmental or mixed in origin, though the exact cause is identifiable in only 40–60% cases.

Mild to moderate ID is usually idiopathic or familial (*? polygenic*), with recurrence risk of ~40% if both parents are affected and ~20% if only one parent is affected. Down syndrome is the commonest genetic cause of ID in Indian children.

Clinical presentation: Severe or profound ID is easily identified in early infancy due to delayed milestones. However, mild to moderate cases are often missed till school-entry or even later age. Important early indicators of ID include:

a. Developmental delay on early surveillance,
b. Neurosensory deficits, e.g. cerebral palsy, visual/hearing defects, language delay, etc.
c. Behavioral problems, e.g. attention-deficit, hyperactivity, impulsivity, etc.
d. Poor scholastic performance.

Presence of physical stigmata, discussed in Ch 3.5 on development delay suggests higher risk of ID and points toward the probable cause **(Table 3.9)**.

Diagnostic evaluation of ID involves: (a) confirmation of diagnosis, (b) identification of underlying etiology and (c) identification of limiting neurosensory defects.

Step I. Confirmation of diagnosis: ID is a shattering diagnosis for parents and should be made only after careful assessment. Single assessment may be abnormal due to temporary variability in performance or environmental influences and an abnormal observation needs to be re-confirmed before disclosing the diagnosis to parents. Other causes for poor performance on IQ testing, e.g. hearing or visual defects should also be considered to eliminate secondary delays in development.

Intelligence quotient (IQ) is a ratio (mental age/chronological age × 100), commonly used to denote presence and severity of ID. It may be assessed by a number of age-appropriate tests to evaluate various domains of cognitive and adaptive behavior, with due consideration for ethnic and linguistic variations as well as adequacy of sensory inputs, e.g. hearing and vision.

In India, commonly used IQ tests include *Wechsler intelligence scale for children for children aged* 6–16 years and *Wechsler adult intelligence scale for those above* >16 years. Adaptive skills are generally tested using *vineland adaptive behavior scale*.

Wechsler intelligence scale for children (WISC) is the most commonly used intelligence test for school children (6–17 years), which can be completed without needing the child to read or write. Current WISC-V version takes ~45–65 minutes to administer and generates a full scale IQ that represents a child's general intellectual ability. It also provides five primary index scores, (i.e. verbal comprehension index, visual spatial index, fluid reasoning index, working memory index and processing speed index) in separate cognitive domains. Many Indian adaptations for WISC, e.g. *Malin's* or *Mahindrika Bhat's tests* are available commercially for use in Indian children >5 years of age.

Step II. Etiological diagnosis is often difficult, though every effort should be made to identify preventable/treatable causes. Important steps in etiological diagnosis are same as for developmental delay and include:

a. *Detailed history,* with special reference to similar family history (pedigree analysis), consanguinity, adverse antenatal/perinatal events and behavioral problems.
b. *Physical examination* with special reference to anthropometry, physical stigmata **(Table 3.9)**, vision/hearing problems and neurological signs. Ophthalmic examination is highly informative in etiological diagnosis of ID, e.g. chorioretinitis in intrauterine infections, cherry-red spot in neurodegenerative disorders, papilledema in hydrocephalus, etc.
c. *Relevant investigations,* depending on suspected etiology, mainly include cytogenetic, biochemical and neuroimaging tests **(Table 3.10)**.

d. *Family screening:* Once a genetic diagnosis is firmly established in the index case, parents and siblings should be screened for computing the recurrence risk and genetic counseling.

Step III. Identification of function-limiting defects, i.e. hearing and vision defects, neuromotor problems, seizures, behavioral problems, parent–child relationship, etc.

Management: Except for a few conditions like hypothyroidism, phenylketonuria and lead intoxication, the majority of disorders with ID have no specific curative treatment. Hence, the *primary aim of management is to maximize functional independence,* e.g. activities of daily living household chores, social independence, etc., *and eliminate limiting factors*, e.g. vision or hearing correction.

Management and rehabilitation program of each child needs to be individualized, according to their needs and potential **(Table 3.11)**. A multidisciplinary team approach is essential in these cases, involving following interventions:

a. Physiotherapy/occupational therapy for neuromuscular dysfunctions
b. Management of associated deficits, e.g. hearing, vision and speech delay, seizures, etc.
c. Psychotherapy or behavioral modification
d. Family counseling and social support
e. Schooling, preferably in regular schools except in severe/profound cases.
f. Institutionalization is the last resort, often needed in severe/profound ID.

Prevention of ID and associated handicaps may be broadly divided into:

I. Primary prevention includes following interventions in all prospective mothers:

a. *Pre-conceptional* measures, e.g.
   - Control of goiter in adult population
   - MMR immunization in girls
b. *Antenatal* measures, e.g.
   - Serological screening for intrauterine infections
   - Folic acid supplements for neural tube defects
   - Anti-D prophylaxis in Rh-negative mothers
   - Appropriate obstetrical and neonatal care
c. *Neonatal screening* for hypothyroidism, PKU, etc.

II. Secondary prevention includes prenatal diagnosis and genetic counseling in cases with family history of ID in parents or previous siblings. Familial ID is usually multi-factorial in origin with recurrence risk of ~20–40%. Although prenatal diagnosis is difficult in these cases, prenatal genetic studies may be used to avoid recurrence of other genetic/chromosomal defects.

III. Tertiary prevention includes minimization of functional handicaps in established ID by early diagnosis and treatment of limiting factors.

IV. Legislative support: ID has been included as a disability under *the Disabilities Act, 1995* that provides for screening of children at-risk, awareness campaigns via mass media and improved perinatal care. It also provides for free education, research and setting up of special teacher's training institutes

3.7 LEARNING DISORDERS

Learning disorders or disabilities (LD) include a large and heterogeneous group of low severity-high incidence disorders, all characterized by "*persistent difficulties in coping with academic skills (learning) due to problems with efficient reading (Dyslexia), writing (Dysgraphia), calculations (Dyscalculia) or in other processing functions, which contribute to learning and are not caused by low intelligence quotient (IQ), visual/hearing handicaps or extraneous factors like parental education and family environment*". These children are not intellectually disabled and have normal or even above average IQ.

Prevalence: Although frequently underdiagnosed, LDs are estimated to be present in ~5–15% of Indian school children, almost six times more common in boys than in girls.

Pathogenesis: Achievement of academic skills requires normal development of many domains including: (a) attention span, (b) cognitive function, (c) memory, (d) speech and language, (e) neuromotor coordination, (f) visual-spatial capability, (g) temporal-sequential order, and (h) personal–social relationship.

Children with LDs have abnormalities in either all (*generalized learning disorders*) or some of these fields (*specific learning disabilities or SLDs*).

Etiology: Exact etiology of LDs is difficult to ascertain in majority of cases, though some inherent or environmental factors have been associated with higher risk, as follows:

a. *Prenatal factors*, e.g. maternal malnutrition, smoking, alcoholism, intrauterine infections and placental insufficiency, e.g. toxemia, etc.
b. *Perinatal complications*, e.g. birth asphyxia, hypoglycemia, hyperbilirubinemia, etc.
c. *Postnatal problems*, e.g. malnutrition, anemia, head injury, lead poisoning, drugs, e.g. anticonvulsants, chronic infections and illnesses, e.g. epilepsy.
d. *Genetic defects*, e.g. Down syndrome, Turner syndrome, Klinefelter syndrome, Fragile X syndrome, Duchenne muscular dystrophy, phenylketonuria, etc.

About 25–65% dyslexic children have a parent or sibling with dyslexia. Some of them have been identified to have under-activation of posterior brain regions and overactivation of anteroinferior frontal regions during the reading process.

Clinical presentation: LDs in children mainly include three different types of presentations-dyslexia (70–80%), dysgraphia (30–40%) and dyscalculia (15–20%), with frequent overlapping or co-existence.

Dyslexia (Reading disability) is the commonest SLD, characterized by *persistent, unexpected difficulty in reading in children or adults*, who otherwise possess normal intelligence, motivation and opportunities to learn. Proper comprehension of written and oral words requires *phonetic processing*, i.e. segmentation of each word into smaller units, before central decoding. Dyslexic children lack this ability of segmentation, leading to slow and incorrect reading, skipping words and lines or substituting common phonetic words. These children like to listen to stories but find it difficult to read them. Dyslexia usually manifests when the formal reading starts, i.e. in first standard of the school, when the focus is on reading to learn than on *learning to read*.

Dysgraphia (Writing disability) presents with problems in hand-writing, e.g. frequent errors in spellings, grammar and sentence formation and shape and size of written alphabets. Children have difficulties in copying from the board and often produce a disorganized text that is difficult to follow. Dysgraphia is almost always associated with dyslexia and is usually not recognized till II/III standard of the school, when written work increases.

Dyscalculia (Mathematical disability) is usually picked up last in V/VI grade or even later, when complex calculations are introduced in schools. Dyscalculia presents with problems in identifying numbers, retrieving arithmetic combinations and understanding language of mathematics, e.g. numbers and symbols. Students may reverse numbers or make errors while reading them aloud.

These problems are usually seen in conjunction with dyslexia or dysgraphia, Mathematical calculations require ability to understand words associated with arithmetic operations and word problems, which can aggravate difficulties in acquiring mathematical skills.

Other types of SLDs, e.g. *dysorthographia* denote spelling difficulties and *dysnomia refers to* difficulty in finding correct word/s for expression. Uncommon LDs includes *auditory processing disorders* (difficulty to comprehend sounds), *language processing disorders* (difficulty to understand spoken words), *non-verbal learning disabilities* (difficulty to understand non-verbal clues) and *visual perceptual deficits* (difficulty to understand visual clues).

Some children with LDs also have ***comorbidities,*** e.g. *problems in attention span* (attention-deficit hyperactivity disorder), *neuromuscular coordination* (Apraxia) and *personal-social adjustments* or social communication disorders (autism spectrum disorders). Many of them also develop secondary behavioral problems, e.g. frustration, low self-esteem, anxiety neurosis and ticks.

TABLE 3.12: Early indicators of learning disabilities

- **Pre-school**
  - Delayed language development
  - Difficulties in learning colors, shapes, etc.
  - Difficulties in learning alphabets, numbers, etc.
  - Problems in pronunciation
- **Early-school**
  - Slow development of vocabulary
  - Repeated spelling mistakes in reading/writing
  - Letter reversals (b/d), inversions (m/w), etc.
  - Problems with left-right discrimination
  - Illegible hand writing
- **Late-school**
  - Difficulty in rhyming words
  - Difficulty in written expression
  - Difficulty in calculations

Diagnosis: LD is a leading cause of poor school performance and the role of school-teachers is vital in early recognition and referral of these children as also the role of pediatrician to guide parents correctly. Some common indicators for suspecting LD in a child are listed in **Table 3.12**, though it can be diagnosed only after the formal education starts or later, provided there is evidence of onset during the years of formal schooling.

Assessment for LD should begin with assessment of– (a) educational history and (b) class-room activities, (c) Intelligence Quotient, (d) visual and hearing functions, followed by, (e) formal psychometric (processing and learning ability) testing.

Formal evaluation of these children involves a battery of specific tests, e.g. *Woodcock-Johnson test of achievement*, *Wechsler individual achievement test*, etc. or locally developed tests, e.g. *National Institute of Mental Health and Neurosciences (NIMHANS) index*. NIMHANS index test differs for children aged 5–7 years (Level I) and 8–12 years (Level II) and has the advantage of availability in Hindi and some regional languages apart from in English.

However, before interpreting these tests, it is important to ensure that these children have:

a. Normal Intelligence Quotient (IQ) on standard IQ tests,
b. Normal visual and hearing functions on relevant assessments,
c. Tests are administered in the language that they understand

Management of LDs requires cooperation from child, parents, peers and school teachers and should involve school counsellors, pediatricians, psychologists, psychiatrists, social workers and education consultants. Important principles of management of these cases

include (a) parental counselling, (b) remedial education, (c) curriculum modification, (d) bypass strategies with strengthening of un-affected skills, (e) accommodative provisions during teaching and examinations.

Schooling: While these children have problems in coping with routine pace of learning, it is preferable to continue regular schooling with suitable modifications, e.g. small-group teaching by specially trained teachers (Special educators) rather than to shift them in special schools. Teachers should be sensitized about the limitations and needs of a child with LD. Under the Right to Education (RTE) Act, all SLD children should be taught in regular schools with provision of a special educator in each school.

Remedial education includes: (a) assessment of the child's strengths and weaknesses in academic skills, (b) altering the pace and mode of teaching, (c) development of an individualized education program with well-defined short-term and long-term goals, (d) and monitoring the child's progress. Interventional sessions, (*i.e.*, twice-or thrice-weekly) could be offered in the school or outside regular school hours. The key is to monitor significant time-bound progress in the child's academic skills and social behavior and confidence.

Accommodation provisions help an older child with: (a) permission to use calculators, (b) *extra time* to complete the task or test, (c) *no deduction* of marks for grammar/spelling mistakes, (d) permission to use a writer during examinations, (e) provision for grace marks. Many educational boards provide these provisions to LD children which vary from one State of India to another.

Teaching strategies: Teachers as well as parents need to be adopt the some strategies in class room and at home, as follows–(a) review the information about previous lesson, before beginning a new lesson; (b) clearly state what the student is expected to learn during each lesson; (c) describe how the student is expected to behave during the lesson, *e.g.* not to talk with peers if the assigned task is found to be difficult, but to raise his/her hands to get the teacher's attention; (d) state all materials that the child will need during the lesson, e.g. crayons, scissors and colored paper for an art project rather than leaving the child to figure out the need of materials; (e) psycho-educational interventions, e.g. seating the child near the teacher to minimize classroom distractions, etc.

In recent *Rights of Persons with Disability Act 2016*, LD has been included and recognized as a disability.

Prognosis: Learning disabilities persist throughout life, though it is usually possible to achieve adequate academic skills and school performance with appropriate teaching and learning techniques. The child's social and emotional well-being should also be prioritized.

3.8 HEARING DISORDERS

Hearing is the essential sensory pathway for development of speech and presence of even mild hearing loss in early childhood may affect speech, learning and psychosocial development.

Severity of hearing loss is categorized on the basis of *unperceived* sound decibels (db), as mild (16–30 db), moderate (31–50 db), severe (50–70 db) and profound (>70 db), i.e. a child with profound hearing loss cannot hear a sound even as loud as 70 db and can hear sounds only louder than 70 db normal conversational speech produces ~55 db of sound.

Incidence: Moderate to severe hearing loss is estimated to be present in ~0.1–0.5% children, apart from a larger number of undetected cases with mild hearing impairment. Less than 10% of hearing impaired children have severe or profound deafness.

Etiology: Common causes of hearing impairment **(Table 3.13)** are broadly classified into 4 groups:

a. ***Conductive hearing loss*** (CHL) due to interference in the mechanical transmission of sounds to the inner ear. These disorders respond well to treatment.
b. ***Sensorineural hearing loss*** (SNHL) due to damage to the cochlea or the auditory nerve. These disorders are usually irreversible. Most cases of congenital hearing loss are sensorineural hearing loss in nature and genetic in origin. Mutations of a single gene GJB2 may be responsible for over 50% cases of congenital SNHL.
c. ***Mixed hearing loss,*** where early treatment of CHL is necessary to minimize the disability.

TABLE 3.13: Common causes of hearing loss

A. Conductive hearing loss
- Congenital anomalies of middle ear
- Acquired defects:
  - *Ear canal:* Otitis media, foreign body, cerumen
  - *Tympanic membrane:* Perforation, sclerosis
  - *Ossicles:* Cholesteatoma, otosclerosis, tumors

B. Sensorineural hearing loss
- *Pre-natal causes:*
  - Familial
  - *Genetic:* Pendred syndrome, Alport syndrome
  - *Congenital* cochlear anomalies
  - *Intrauterine (TORCHS) infections*
- *Post-natal causes:*
  - *CNS infections:* Meningitis, encephalitis
  - *Trauma:* Head injury, noise trauma, surgery
  - Tumors and lesions of VIII cranial nerve
  - *Drugs:* Aminogycosides, quinine
  - *Toxins:* Lead poisoning

C. Central auditory problems
- Cerebral palsy
- Mental retardation

***TORCHS:** Toxoplasmosis, rubella, CMV, herpes, syphilis

d. ***Central auditory problems:*** These children have normal propagation of auditory stimuli to central auditory areas, but further processing, i.e. comprehension of spoken words, is impaired. Audiograms are typically normal in these cases.

Clinical presentation and age of diagnosis depends on the severity and type of hearing loss as well as whether it is unilateral or bilateral. Lack of startle response in the newborn to a sound is often the earliest indicator of hearing impairment, apart from others listed in **Table 3.14**. Unilateral hearing defects lead to problems in localizing the source of the sound.

Diagnosis of hearing problems depends on routine screening of high-risk cases or on clinical suspicion of hearing impairment, with following age-appropriate tests:

a. *Oto-acoustic emissions* (OAE) *test* is a simple bed-side screening test to assess neonatal screening, though with poor sensitivity. It is performed by a special machine, placing the small probe in the newborn's ear canal. When the machine triggers a click sound, sound waves travel from the external ear to inner ear and cause outer hair cells of the cochlea to move, producing sound detected by the probe. It indicates normal cochlear function.

b. *Audiometry brain stem response (ABR)* is the more reliable screening test to assess the hearing function in infants and to differentiate the high-tone deafness (SNHL) from low-tone deafness (CDL). Various types of audiometric evaluations, suitable for different age groups include-behavioral response audiometry (<6 months), visual reinforcement audiometry (6 months–3 years), play audiometry (3–5 years) and Pure-tone audiometry for children > 5 years.

Brainstem evoked response audiometry (BERA) is the most reliable test for early diagnosis of hearing loss even in newborns.

TABLE 3.14: Indications for hearing assessment

A.	**Presence of high-risk factors** • Family history of hearing impairment • *High-risk neonates:* Preterm, asphyxia, hyperbilirubinemia • Craniofacial anomalies • Cerebral palsy or mental retardation • *CNS infections:* Meningitis, encephalitis • Chronic otitis media
B.	**Clinical suspicion of deafness** • No startle response at birth • No turning of head towards the sound by 3 months • No response to name-call by 10 months • No response to gesture-free command by 18 months • Delayed language development • Learning disabilities/poor school performance.

c. *Impedance audiometry* helps to check patency of eustachian tube, tympanic membrane and ossicles by tympanometry, acoustic impedance testing and measurement of acoustic reflex thresholds.

d. *Local examination* of ear canal and testing of air vs. bone conduction by tuning-fork tests (*Rinne's* and *Weber's tests*) helps to distinguish CHL from SNHL. In CHL, bone conduction is better than air conduction, while both are affected in SNHL.

Management: Early diagnosis and appropriate management of hearing impairment is essential for normal speech development. Children given hearing aids before 6 months of age develop better speech than untreated children or those given hearing aids later. Principles of management include:

- Correction of CHL etiology, e.g. otitis media;
- Correction of SNHL by hearing aid or cochlear implants for sound amplification;
- Communication training with use of non-verbal methods, e.g. sign-language, lip-reading, etc.;
- Modified schooling, e.g. seating them on front benches or in special schools;
- Psychological and behavioral counseling for child, parents and teachers.

Prevention: Prevention of congenital deafness has been included as a disability for early identification and remedial action under *Rashtriya Bal Swasthya Karyakram* (RBSK) by screening of infants and children under age 18 years by a mobile team and provision of appropriate treatment at District Early Intervention Centres.

Indian Academy of Pediatrics recommends universal screening of newborns for hearing impairment by a two-step process, as follows:

- All newborns should be screened before the discharge from hospital with OAE and if it 'fails', should be repeated after 4–6 weeks during first immunization visit. If OAE fails again, then, these infants should be subjected to behavioral response audiometry (BERA).
- All babies admitted to intensive care unit should be directly screened *via ABR*.
- All babies with abnormal ABR should undergo detailed evaluation, hearing aid fitting and auditory rehabilitation, before six months of age.

The goal is to screen all newborn babies before one month, diagnose hearing loss before three months and start intervention before six months of age.

3.9 SPEECH AND LANGUAGE DISORDERS

Communication is the exchange of thought, words and ideas between two or more individuals. **Speech** is the communication in an audible (verbal) form. **Language** denotes the knowledge of rules for communication.

Language is a function on which the speech is constructed. Normal development of speech requires- (a) normal hearing, (b) normal neurological functions to understand, process and formulate appropriate response, and (c) normal motor structures and neuromuscular coordination required for phonation. In addition, stimulative social and emotional nurturing in the environment is also essential for development of verbal skills and language.

Etiologically speech disorders may be primarily due to **(Table 3.15)**:

a. *Disorders of receptive language*, e.g. hearing impairment, (commonest cause in children).
b. *Disorders of central processing*, e.g. CNS disorders,
c. *Disorders of expressive language* due to orofacial or phonation problems.

Clinically, expressive speech disorders may be broadly classified as follows, though many patients have multiple defects.

a. ***Resonance disorders:*** Hyper/hyponasality.
b. ***Voice disorders***: Abnormal pitch/quality of voice.
c. ***Fluency disorders:*** Stuttering, stammering, etc.
d. ***Articulation disorders***, e.g. imprecise production of sounds, e.g.
   - *Substitution*, i.e. replacement of one sound with another, e.g. height for light.
   - *Omission*, i.e. failure to produce some sounds, e.g. boo. for book.
   - *Distortion*, i.e. inappropriate sounds replacing the correct one.
e. ***Language disorders***, i.e. problems in formulation of proper language, e.g.
   - *Telegraphic speech*, i.e. inability to form sentences.
   - *Word-finding disorders*, i.e. difficulty to name a picture or in the use of gestures to explain it.
   - *Narration disorders*, i.e. inability to describe an experience or tell a story.

TABLE 3.15: Causes of speech/language delay

- ***Hearing loss*** since birth or early infancy
- ***Central processing defects***
  - Mental retardation or learning disorders
  - Autistic spectrum disorders
  - Post-meningitic/encephalitic sequelae
- ***Phonation organ defects***
  - *Structural:* Cleft palate, adenoid hypertrophy
  - *Neuromuscular:* Cerebral palsy, bulbar palsy
  - *Breathing disorders:* Chronic lung diseases
- **Environmental factors**
  - Speech problems in parents
  - Emotional deprivation
  - Bi-lingualism

Diagnosis: *Early warning signals* for speech problems in a baby include:

1. Does not babble by 6 months
2. Does not speak monosyllables by 9 months
3. Does not speak > 3 words by 18 months
4. Does not speak 2 word meaningful phrases by 2 years
5. Excessive meaningless (jargon) speech beyond 2 years
6. Does not speak simple meaningful sentences by 3 years
7. Stutters beyond 4 years
8. Any speech sound error beyond 7 years
9. Presence of pitch abnormalities at any age.

Management: Presence of speech defects needs careful evaluation, intervention and follow-up, as many of them are easily manageable. Principles of management include:

- Correction of hearing impairment, etc.
- Speech and phonation therapy,
- Training in alternate modes of expression, e.g. sign language, etc. and
- Behavioral support and counselling.

3.10 SCHOLASTIC BACKWARDNESS

Scholastic performance of a child is the measure of achievement in academic field. Unrecognized and unresolved scholastic backwardness leaves a life-long impact on the future, affecting educational achievements, employment prospects and behavioral performance.

Prevalence of scholastic backwardness in India is uncertain due to poorly defined criteria for diagnosis but estimated to be in the range of ~20–30%, being the common cause of school drop-outs.

Etiology is multi-factorial, ranging from subtle learning disabilities to frank intellectual disability or presence of function-limiting hearing/vision impairment. Environmental factors and general health of the child are also major determinants of academic performance **(Table 3.16)**.

TABLE 3.16: Causes of scholastic backwardness

Primary (organic)

- Intellectual disability
- Learning disorders (dyslexia)
- Attention-deficit hyperactivity disorder
- Visual or hearing impairment
- *Systemic:* CNS disorders, hypothyroidism
- *Drugs:* Anticonvulsants, substance abuse
- *Toxins:* Lead or aluminium poisoning

Secondary (environmental)

- *Family:* Lack of encouragement, stress
- *School:* Inappropriate teaching methods poor student–teacher relationship
- Emotional, e.g. frequent school changes
- Behavioral disorders
- Frequent school absenteeism
- Chronic diseases, e.g. asthma, epilepsy

Assessment: While scholastic performance is objectively reflected in the examination results, school teachers and parents are in best position to identify ***early warning signs*** of scholastic difficulties, e.g.:

a. Avoidance to go to school or *school phobia*,
b. Reluctance to volunteer for reading/writing activities in the class,
c. Tendency to misread/misinterpret information,
d. Difficulties in reading, writing, spelling, mathematical calculations, etc. and
e. Development of behavioral problems, e.g. frustration, aggression, defiance, etc.

A child struggling with scholastic backwardness needs early identification and comprehensive evaluation including: (a) assessment for vision and hearing, (b) general intelligence testing (IQ), (c) formal testing for learning disabilities (Ch 3.7) and (d) search for environmental factors, e.g. socioeconomic and emotional reasons, which are preventing them from achieving their full potential.

Scholastically challenged children with normal IQ scores usually have *learning disabilities*, while those with IQ ranging from 70–89 are considered as *slow-learners*. Those with lower IQ scores (<70) are likely to have intellectual disability.

Management depends on the identified cause, with non-pharmacotherapeutic management being the key. All children and families can be benefitted by a well-planned dynamic program using modalities of remedial education, life-skill training, management of comorbidities and provision of appropriate family/community support. Pharmacotherapy is useful for management of comorbidities. The physician's role as the "*conductor of this orchestra*" of support is vital as part of the journey of each family.

3.11 AUTISTIC SPECTRUM DISORDERS

The term *autistic spectrum disorder* refers to a range of clinically similar disorders with variable severity, all characterized by a *diad* of: (a) impaired social communication and interaction, and (c) rigid, repetitive or obsessive behavior.

Earlier terms of childhood autism, infantile autism, Asperger's disorder, pervasive developmental disorders are now all included under the umbrella of autistic spectrum disorders.

Incidence: While reported incidence of autism in India is in ~1 in 65 children aged 2–9 years, under-diagnosis is common and incidence seems to be rising due to increasing awareness. Autism is 3–4 times more common in males and in high socioeconomic strata, perhaps due to better chances of detection.

Etiology is not well established though ASDs are frequently associated with: (a) family history, (b) chromosomal disorders, e.g. fragile X chromosome, (c) genetic disorders, e.g. phenylketonuria, (d) intrauterine infections, e.g. rubella, (e) congenital brain malformations, e.g. hydrocephalus, and (f) postnatal encephalitis, meningitis and infantile spasms. Familial or genetic predisposition is supported by ~ 80% and 20% concordance rate in monozygotic and dizygotic twins.

Clinical features: Autistic children are often mistaken as "*good babies*" in infancy, as due to poor social interaction, they do not demand much attention. Average age of diagnosis in Indian children is ~3–6 years, though reliable diagnosis can be made as early as 18–24 months of age. Infants who demonstrate echolalia or abnormal hand movements or spinning, etc. should be evaluated for Autism spectrum disorder. Delayed development of verbal and non-verbal communication is usually the initial parental concern in second year of life, with gradual recognition of typical features, as follows:

a. *Impaired social interaction:* These children do not show any interest in their parents and do not make friends. They are withdrawn, spend hours in solitary play, often preoccupied with trivial objects, e.g. buttons or parts of their own body.
b. *Impaired communication with* lack of both, verbal as well as non-verbal communication skills. Even after the development of speech, they are unable to sustain a conversation and have other abnormalities, e.g. echolalia, pronominal reversal, nonsense rhyming, etc.
c. *Stereotype behaviors*, i.e. inordinate desire for *sameness* with rigid interests and repetitive or obsessive activities. These children tend to play for many hours with one object, alone, and do not want to be disturbed.
d. *Associated behavioral problems*, e.g. hyperactivity, short attention span, impulsivity, aggressiveness, temper tantrums are common. Most of them have odd responses to sensory stimuli, e.g. higher pain threshold or over-sensitivity to touch, sound, light, odors, etc.

Intelligence is almost always affected with average IQ of <70 in most cases and many cases have seizures or associated problems, e.g. abnormal gait, toe-walking, etc.

Diagnosis of autism is essentially clinical, based on the DSM V criteria **(Table 3.17)**. However, the assessment of its severity and presence of co-existing abnormalities require: (a) comprehensive assessment of hearing, speech and language, (b) periodic evaluation for cognitive functions (IQ testing), social adjustment, verbal and non-verbal communication, (c) evaluation for secondary behavioral disorders.

Indian Academy of Pediatrics (IAP) recommends that:

a. All children should be screened by a standardized autism screening tool at 18 and 24 months of age, e.g. Modified Checklist for Autism in Toddlers (M-CHAT-R™) **(Table 3.18)**.

TABLE 3.17: Diagnostic criteria for autism (DSM V)*

A. Persistent deficit in social interaction (All four)
- **Deficit in social-emotional reciprocity**
  - Abnormal social approach,
  - Failure of normal back-and-forth conversation
  - Poor sharing of emotions/interests
  - Failure to initiate/respond to social interaction
- **Deficit in normal verbal communication**
  - Poor eye contact or body language
  - Deficit in understanding/use of gestures
- **Deficit to develop/ maintain relationships**
  - Difficulty in adjusting behavior with social context
  - Difficulty in sharing imaginative play
  - Difficulty in making friends

B. Restricted and stereotype behavior (At least two)
- Stereotype, repetitive motor movements/ speech
- Insistence on same, rigid routine
- Restricted, fixed interests (attachment to objects)
- Hyper-/hypo- reactivity to sensory inputs, e.g. indifference to pain, visual fixation with lights

C. Symptoms since early childhood, though masked

D. Symptoms causing significant functional impairment

E. Not explained by intellectual disability or other causes

*Modified for brevity.
Severity for criteria A and B must be described in 3 levels:
Level 3 – requires very substantial support,
Level 2 – requires substantial support, and
Level 1 – requires support.

b. If the screening test is positive, they should be referred for expert and comprehensive evaluation assessment and timely initiation of intervention. Indian Scale for Assessment of Autism (ISAA) or Childhood Autism Rating Scale (CARS) are commonly used tools to confirm the diagnosis.
c. Children <18 months should also be evaluated for social communication skills and must be followed up, till formal screening

M-CHAT-R™ is a simple and freely available screening tool for ASD in toddlers between 16 and 30 months of age **(Table 3.18)**. As a screening tool, M-CHAT-R™ aims to maximize sensitivity and detect as many cases of ASD as possible and hence, has a high false-positive rate. A follow-up test (M-CHAT-R/F™) is also available for borderline cases, though no child should be diagnosed as ASD on the basis of M-CHAT alone (which is only a screening test), but must be referred for further assessment.

D/D of autism includes other cause of inattentiveness and poor communication, e.g. deafness, intellectual disability, developmental language disorder, childhood schizophrenia and attention-deficit hyperactivity disorder.

Rett syndrome is a rare, X-linked disorder, almost exclusively seen in females (lethal in males), characterized by normal development till 6–12 months, followed by regression of motor and linguistic milestones, secondary microcephaly, and stereotyped hand movements, e.g. hand-wringing.

Management of autistic children is a long process and aims to achieve as much functional independence as possible and requires a multi-disciplinary team approach involving pediatrician, developmental pediatrician, psychologist, occupational therapist, speech therapist, special educator, etc.

Intervention should begin as early as possible, even while confirmation of the diagnosis is in progress and should be specific, evidence-based, structured and appropriate to the developmental needs of the child.

Aims of the management have to be realistic and include:
a. Enhancing eye contact, social orientation, nonverbal and verbal communication,
b. Reducing repetitive/restricted behaviors, sensory issues and hyperactivity, and
c. Improving social, motor, and behavioral capabilities. Many good interventional models are in use for these children.

Important components of management include:
a. ***Pharmacotherapy,*** though not curative, is a valuable tool to control certain symptoms. Choice of drug depends on predominant symptoms and includes: (a) Methylphenidate to control hyperactivity (PO 10–40 mg/day in morning), (b) Atomoxetine (PO 1.2 mg/kg/day) , if methylphenidate is not tolerated, (c) Risperidone to control aggressive and self-injurious behavior (PO 0.5–3.5 mg/day), (d) Fluoxetine to control repetitive and rigid behaviors (PO 2.4–20 mg/day), and (e) Melatonin (PO 0.5–1. mg/day) before bed-time for insomnia. Other drugs may be required for co-morbidities, e.g. anxiety, mood disorders, etc.
b. ***Play therapy, language therapy and behavior therapy*** using operant conditioning, have shown promising results in some cases as also psychotherapy in children with at least some communication.
c. ***Educational management:*** While inclusive education is the ideal goal, it needs to be rationalized and based on individual situation. An appropriate individualized educational plan should reflect accurate assessment of the child's strengths and vulnerabilities and their relation to academic skills. Curriculum modification may be required to meet the education needs and capabilities of the child. Individualized planning for education and imparting practical skills should be made.
d. ***Family therapy*** is required for parents to understand the problem and cope with the stress of the illness. Currently, many support groups involving affected parents, health professionals and voluntary organizations are working in India for this purpose.
e. ***Disability support:*** Under the Disability Act 1999, ASD is recognized as a disability, after certification by a designated Autism Certification Medical Board.

TABLE 3.18: M-CHAT- R™

*Please answer these questions about your child. Keep in mind how your child usually behaves. If you have seen your child do the behavior a few times, but he or she does not usually do it, then please answer **no**.*

1.	If you point at something across the room, does your child look at it? *(e.g. if you point at a toy or an animal, does your child look at the toy or animal?)*	Yes/ No
2.	Have you ever wondered if your child might be deaf?	Yes/ No
3.	Does your child play pretend or make-believe? *(e.g. pretend to drink from an empty cup, pretend to talk on a phone, or pretend to feed a doll or stuffed animal?)*	Yes/ No
4.	Does your child like climbing on things? *(e.g. furniture, playground equipment, or stairs)*	Yes/ No
5.	Does your child make unusual finger movements near his or her eyes? *(e.g. does your child wiggle his or her fingers close to his or her eyes?)*	Yes/ No
6.	Does your child point with one finger to ask for something or to get help? *(e.g. pointing to a snack or toy that is out of reach)*	Yes/ No
7.	Does your child point with one finger to show you something interesting? *(e.g. pointing to an airplane in the sky or a big truck in the road)*	Yes/ No
8.	Is your child interested in other children? *(e.g. does your child watch other children, smile at them, or go to them?)*	Yes/ No
9.	Does your child show you things by bringing them to you or holding them up for you to see – not to get help, but just to share? *(e.g. showing you a flower, a stuffed animal, or a toy truck)*	Yes/ No
10.	Does your child respond when you call his or her name? *(e.g. does he or she look up, talk or babble, or stop what he or she is doing when you call his or her name?)*	Yes/ No
11.	When you smile at your child, does he or she smile back at you?	Yes/ No
12.	Does your child get upset by everyday noises? *(e.g. does your child scream or cry to noise such as a vacuum cleaner or loud music?)*	Yes/ No
13.	Does your child walk?	Yes/ No
14.	Does your child look you in the eye when you are talking to him or her, playing with him or her, or dressing him or her?	Yes/ No
15.	Does your child try to copy what you do? *(e.g. wave bye-bye, clap, or make a funny noise when you do)*	Yes/ No
16.	If you turn your head to look at something, does your child look around to see what you are looking at?	Yes/ No
17.	Does your child try to get you to watch him or her? *(e.g. does your child Yes No look at you for praise, or say "look" or "watch me"?)*	Yes/ No
18.	Does your child understand when you tell him or her to do something? *(e.g. if you don't point, can your child understand "put the book on the chair" or "bring me the blanket"?)*	Yes/ No
19.	If something new happens, does your child look at your face to see how you feel about it? *(e.g. if he or she hears a strange or funny noise, or sees a new toy, will he or she look at your face?)*	Yes/ No
20.	Does your child like movement activities? *(e.g. being swung or bounced on your knee)*	Yes/ No

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For all items except 2, 5, and 12, the response "NO" indicates ASD risk; for items 2, 5, and 12, "YES" indicates ASD risk. Following algorithm maximizes psychometric properties of the M-CHAT-R:

- **LOW-RISK (Total Score 0-2)** No further action required unless surveillance indicates risk for ASD. However, rescreen after second birthday, if child is < 24 months old.
- **MEDIUM-RISK (Total Score 3-7)** Administer M-CHAT-R/F (Not included here). If the remains at 2 or higher, child has screened positive and refer for further evaluation. If score on follow-up is 0-1, child has screened negative and no further action required unless surveillance indicates risk for ASD. Child should be rescreened at future visits.
- **HIGH-RISK:** Total Score is 8-20; refer immediately for diagnostic evaluation and eligibility evaluation for early intervention.

Prognosis: Autistic children, reared in a positive environment, show some improvement during early school years. However, symptoms tend to aggravate during adolescence with deterioration in behavioral and cognitive skills, additional psychiatric problems and appearance of epilepsy, especially in girls. As sexual drive increases, they may indulge in embarrassing behaviors.

Absence of communicative speech till 5–6 years of age indicates poor prognosis.

3.12 ATTENTION-DEFICIT HYPERACTIVITY DISORDER

Attention deficit hyperactivity disorder (ADHD) is a common disorder in children, characterized by three core-groups of age-inappropriate symptoms:

a. Hyperactivity,
b. Impulsivity, and
c. Inattentiveness;

Leading to secondary problems, e.g. poor scholastic performance, conduct disorders, emotional and social maladjustment, etc.

While some children have all three components of ADHD, others manifest with abnormalities in only one or two fields. Accordingly, three major types of ADHD are recognized:

a. ADHD, combined type (~60–70%)
b. ADHD, predominantly inattentive type (~25–30%)
c. ADHD, predominantly hyperactive/impulsive type (~8–10%)

Prevalence: Reported prevalence of ADHD varies according to diagnostic criteria, awareness among health professionals and cultural norms of the community. Frequently under diagnosed, ADHD is estimated to be present in ~10% of Indian children, with striking preponderance in boys (4–6:1). Boys are more likely to be hyperactive/impulsive, while girls are usually inattentive.

Pathology: *Hypoplasia and hypofunctioning of frontostriatal system* is considered as the key pathological defect in ADHD, with altered balance between two important neurotransmitters that modulate attention, mood and movements-neuroinhibitory *dopamine* and neuro-excitatory *norepinephrine*.

Modern investigative techniques have shown significant structural/functional abnormalities in ADHD children including:

a. smaller volumes of frontal lobes and cerebellum,
b. diminished cerebral blood flow,
c. impaired cerebral oxygen/glucose metabolism, and
d. reduced levels or end-receptor sensitivity of dopamine.

Etiology of ADHD is uncertain, currently thought to be a complex interplay of both hereditary and environmental factors. Some important causative factors include:

a. *Hereditary* seems to play a crucial role in ADHD as ~1/3rd of these cases have similar family history and concordance rate in monozygotic twins is ~75–90%. Genetic studies have implicated defect in several genes, modulating dopamine/norepinephrine action, e.g. D2 receptor gene (DRD2), D4 receptor gene (DRD4), and over-expression of dopamine transporter-1 gene (DAT-1), all located on short arm of chromosome 16.
b. *Environmental factors* seem to be more important in cases without family history. Low birth weight and prenatal exposure to maternal smoking, alcohol/drug abuse and environmental toxins, e.g. lead, dioxins and plastic constituents have been frequently implicated. Other adverse factors in family environment, e.g. psychosocial stress, maternal mental disorder, paternal criminality, low socioeconomic status, etc. have also been linked to the increased risk of ADHD.

Clinical presentations: While the diagnosis of ADHD is usually not made till school entry, most cases have abnormal behavioral traits in earlier life, e.g. excessive crying and disturbed sleep in infancy or even unusual intrauterine activity. Some of them may achieve gross motor milestones at an earlier age.

Hyperactivity/impulsivity is often appreciated earlier (at 4–5 years of age) than inattention (8–9 years). Characteristic core-group manifestations of ADHD are as follows, though all children do not have all components:

a. ***Inattentiveness,*** though commonest manifestation is often overlooked in preschool years and rarely noticed before school age. These children have difficulty in focussing their attention in situations that call for sitting *still*, e.g. classrooms or dinner tables. They can only engage themselves in brief activities and change activities frequently. Children with predominantly inattentive type of ADHD often seem to *drift away* into their own thoughts or lose track of what was going on around them.
b. ***Hyperactivity,*** the commonest cause of parental concern is usually noticed in preschool years as excessive movements, restlessness, fidgety, and shortened attention span. As pre-schoolers by nature have shorter attention span that improves with time, persistence of such behavior beyond 3 years of age is a more reliable indicator of ADHD. Even in older children and adolescents, attention span often depends on the level of interest in a particular activity. Most teenagers can listen to music or talk to their friends for hours but may be less focussed during homework. Hyperactivity tends to increase when child is tired, hungry, anxious or facing a new environment.
c. ***Impulsivity*** is closely associated with hyperactivity and often manifests as a dislike or inability for waiting for his/her turn. They interrupt others in their conversations and some of their actions may be extremely irritating or dangerous. When stimulated, they can quickly get out of control and turn aggressive or abusive.

Comorbidities: Apart from core-group manifestations, ~30–50% of these children have co-existing cognitive, learning and language disorders. Further, most of them develop secondary behavioral problems with advancing age, e.g. oppositional defiant behavior, conduct disorders, antisocial behavior and risk-taking behavior like drug abuse, sexual misconduct, teenage pregnancy, etc. Early identification and appropriate intervention for ADHD may prevent these complications in late childhood/adolescence.

Diagnosis: There is no specific diagnostic test for ADHD and diagnosis is exclusively clinical, based on DSM-V criteria **(Table 3.19)**. It should be noted that:

TABLE 3.19: Diagnostic criteria for ADHD (DSM V)*

A. Age-inappropriate behavior (A-1 or A-2)

A-1 Inattention (6 or more)

1. Fails to attend details/make careless mistakes
2. Difficulty in sustained attention during tasks
3. Does not seem to listen, when spoken directly
4. Does not follow instructions. Fails to finish task
5. Troubles in organising the tasks
6. Avoids tasks requiring sustained mental efforts
7. Loses things, e.g. toys, books, etc.
8. Easily distracted
9. Forgetful in daily activities

A-2 Hyperactivity/impulsivity (6 or more)

1. Fidgets with hands or feet
2. Leaves seat in classroom frequently
3. Runs-about/ climbs in inappropriate situations
4. Difficulty in playing quietly
5. "Often on the go" as driven by a motor
6. Talks excessively
7. Blurts-out answers before question completes
8. Difficulty in waiting for their turn
9. Interrupts or intrudes on others

B. Some symptoms evident <12 years of age

C. Symptoms present in >1 situation (home, school)

D. Symptoms interfere in social/school functions

E. Symptoms not accountable to other pervasive developmental or mental disorder

*All 5 criteria (A-E) should be fulfilled.

Note: Classification of ADHD sub-types:
– Combined type: (both A1 and A2 fulfilled)
– Predominantly inattentive type: (only A1 fulfilled)
– Predominantly hyperactivity/impulsivity (only A2 fulfilled)

a. As many of ADHD symptoms are also commonly present in normal preschool children, diagnosis should be reviewed after repeated evaluation and *preferably kept as provisional till 5 years of age*.
b. Some signs/symptoms of ADHD, e.g. verbal impulsivity and restlessness may not be evident in highly-structured situations, e.g. clinics and their absence does not preclude the diagnosis.

Considering the complex nature of disease, a multi-disciplinary assessment is necessary in all cases of ADHD, including:

a. Detailed perinatal and developmental history,
b. Psychometric testing as well as other standardized rating scales-to be completed by the parents and child's school,
c. Thorough physical examination and developmental assessment,
d. Evaluation for abovementioned diagnostic criteria,
e. Evaluation for co-morbidities or secondary behavioral problems, and
f. Psychosocial evaluation of the family and school environment. Laboratory investigations are indicated only to exclude other causes of hyperactivity/inattention.

TABLE 3.20: Guidelines for parents/teachers in ADHD

- Ensure a regular routine and environment
- Divide his/her work into small chunks
- Provide simple and clear instructions
- Make frequent eye contacts with child
- Allow liberal breaks between the tasks
- *Positive reinforcement:* Praise on task completion
- *Non-accusatory feedback* on task completion
- Avoid overstimulation/fatigue to the child
- Avoid exciting TV programs/games at bed time
- Keep dangerous articles beyond the child's reach
- Be loving but consistent and firm with child
- Encourage peer-relations and teach social skills
- Promote his strengths to build self-confidence

D/D: Although features of ADHD are quite characteristic, transient/persistent hyperactivity or inattention may also be due to: (a) allergies, (b) sleep deprivation, (c) chronic physical disability, (d) sensory impairment, e.g. hearing/visual defects, (d) chronic physical disability, (e) intellectual disability, (f) seizure disorders, e.g. absence seizures, and (g) drug toxicity, e.g. anticonvulsants.

Management aims to improve functional outcomes, e.g. decrease hyperactivity and impulsivity levels, improve social and academic functioning, along with treatment of co-morbid conditions. Effective interventions may be broadly divided into two categories: (a) behavioural management, and (b) pharmacotherapy.

Behavioral management should begin as soon as possible, even in pre-school phase before confirmation of diagnosis and should include: (a) *Positive reinforcement,* e.g. rewarding the child after successful completion of given task, (b) *Negative reinforcement,* e.g. withdrawing a reward after an unwanted behavior, (c) Time-outs, e.g. asking the child to stay away for some time after a unwanted behaviour. Some important guidelines for parents/teachers are given in **Table 3.20**.

Pharmacotherapy is largely needed for older children and should not be started before the confirmation of diagnosis at ~6–7 years of age and the family has been counselled about purpose of medications, i.e. *to control the symptom and not to cure the disease*. Parents should be advised that 2–6 weeks of medication may be needed for any therapeutic effect.

Psychostimulants, e.g. *methylphenidate* (MPH), is the cornerstone of pharmacotherapy in ADHD, which boost and balance the level of neurochemicals, e.g. dopamine and norepinephrine, by facilitating their synaptic release and inhibiting their reuptake. About 70–80% cases show positive response to stimulants as reduced hyperactivity, increased attention span, and improved visual/motor skills. However, these agents do not directly address other problems, e.g. academic failure or social maladjustment.

Dosage and frequency requirements of MPH vary in different children. Usually, therapy should begin with a low dose of PO 5 mg/dose 30 minutes after meals and should be increased gradually to maximum of 60 mg (never >2 mg/kg) according to the clinical effect. The action begins with 20–30 minutes with peak effect at 1–2 hours and lasts for 3–5 hours. Side effects, e.g. anorexia, headache, abdominal discomfort, mood instability and insomnia (MPH should not be given after 4 PM) are common at the onset of therapy but rarely require dosage modifications and disappear after a few days. Other side-effects, e.g. tics or persistent hypertension are rare and may require dose reduction.

Long-term use of MPH is known to cause growth suppression and *intermittent drug vacations* are recommended to minimize growth effects. A child with the predominantly inattentive type of ADHD may need medication only on school days, while a child with difficulty in peer relationships may need it every day. A child who participates in afterschool academics or sports activities on certain days of the week may require longer-acting preparations or more frequent dosing on those days.

Atomoxetine hydrochloride, a non-stimulant norepinephrine transport inhibitor, has been recently established as safe and effective alternative. It should be started with a lower dose of PO 0.5 mg/kg/day for at least first 3 days and gradually increased to maximum 1.2 mg/kg/day. Unlike psychostimulants, which are predominantly useful in hyperactive children, atomoxetine has shown effectiveness in both the inattentive and hyperactive symptoms domains.

Dietary interventions, e.g. elimination of foods considered as allergens, e.g. wheat, milk, eggs, etc. or diets incriminated to increase hyperactivity, e.g. sugar, chocolate and caffeine, etc. are of no proven value, as also the *Fein-Gold* diet (free of additives).

Prognosis: ADHD is incurable but can be managed successfully in most cases. Hyperactivity/impulsivity usually lessens with age, often replaced by other problems, e.g. antisocial behavior and learning difficulties. Inattention tends to persist throughout the life. In general, 30% children show near-complete resolution of symptoms by adulthood, 40% persist with some symptoms but overall adequate functioning and the rest continue to have severe dysfunction with secondary complications, e.g. anti-social behavior. Adults with childhood ADHD have a higher likelihood of emotional and social problems, unemployment, and criminality.

Unfortunately, ADHD is not recognized as a disability under the Disability Act 1999, as of now.

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CHAPTER

4

Behavioral Disorders

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Development of behavior in children is a complex process, influenced by *inherent temperament* as well as *exogenous influences*, e.g. family/social environment and organic brain disorders, e.g. genetic or chromosomal disorders **(Table 4.1)**. Consequently, all children, like all adults, have unique behavioral traits, usually within the acceptable limits of deviance. It is important to differentiate these benign aberrations from more serious behavioral or psychopathic disorders, which require detailed evaluation, expert referral and intensive management.

The term "behavioral disorders" denote a *spectrum of abnormal behavior patterns in children, ranging from transient, minor and essentially benign habit disorders to chronic and debilitating psychiatric illnesses.* While termed as *disorders*, many of these problems in children are mere aberrations in normal behavior, which may disappear with age. Some important and common behavioral problems are discussed in this chapter.

TABLE 4.1: Determinants of child behavior

- **Biologically inherent temperament,** e.g.
  - Easy vs. difficult (fussy) babies
- **Organic causes:**
  - *Chromosomal:* e.g. Klinefelter or Fragile X chromosome
  - *Genetic:* Phenylketonuria
  - Organic brain injury
    - *Prenatal:* CNS anomalies, substance abuse
    - *Perinatal:* Birth asphyxia
    - *Postnatal:* Infections, epilepsy
  - Physical/mental handicaps
- **Environmental causes**
  - *Family factors:*
    - Parental personality, intelligence, education
    - Parent-child bonding (love, rejection, indifference)
    - *Child-caring behavior:* Overprotection/discipline
    - Inconsistent parental behavior (confusion)
  - *Extra-family factors:*
    - Social/economic discrimination
    - Frequent change of schools/ residence
    - Stressful school environment
    - Peer-pressure
    - Effect of mass media, role models
- **Learning and conditioning influences**

4.1 FUSSY INFANT

Fussy infant, while difficult to define, is an *infant who tends to be more demanding or difficult to please*. These babies are often irritable and inconsolable even for minor matters.

Each baby has a different temperament and occasional fussiness is not uncommon, which might be their way to express pain, discomfort or frustration. However, persistent fussiness might be an early sign of more serious underlying problem.

Thomas and *Chess* classified babies in terms of temperament as follows:

- **Easy babies (**40%) who adjust easily to new situations and quickly establish routines. These babies are generally cheerful and easy to calm.
- **Difficult babies (10%),** who are slow to adjust to new experiences and likely to react negatively and intensely to stimuli and events.
- **Slow-to-warm-up babies (15%),** who are somewhat difficult at first but become easier over time.

Temperament of each baby is inherently determined though can be modified to some extent by parents and child rearing practices.

Etiology: All infant may be occasionally fussy due to: (a) *Physical discomfort*, e.g. hunger, wet diapers or diaper rash, lack of sleep, unpleasant hot/cold or noisy environment, (b) *Emotional stress* or frustration, e.g. loneliness, separation from mother, stranger anxiety, or (c) *Feeding difficulties*, e.g. low milk output or nipple confusion often make baby irritable **(Table 4.2)**.

However, persistent fussiness may be a warning signal of more serious underlying health problem and needs to be investigated further before labeling him/her as a fussy infant/child.

Management: Most infants are usually little fussy during early infancy (1–3 months) and no specific intervention is required except: (a) identification and removal of physical discomforts, e.g. hunger, wet diapers, unpleasant environment, etc; (b) exclusion of serious

TABLE 4.2: Causes of fussy infant

- **Physical causes**
  - Hunger/feeding difficulties
  - Wet diapers
  - Unpleasant hot/cold
  - Noisy environment
  - Insect bites
- **Emotional stress**
  - Loneliness, separation from mother
  - stranger anxiety, etc.
  - Overstimulation: Lack of sleep
- **Painful illnesses**
  - Blocked nose
  - Ear infection (Eustachian tube block)
  - Stomach pain, e.g. evening colic
  - Teething/ toothache
  - Gastroesophageal reflex
  - Constipation
  - Undetected injury
  - Headache, CNS infections
- **Developmental issues**
  - Autistic spectrum disorders

or painful underlying illnesses, (c) reassurance to the parents, and (d) training them simple tricks to calm the baby, e.g. cuddling, swaddling, soothing sounds, e.g. humming, gentle rocking or calming motions. However, interventions, e.g. over-feeding or use of pacifiers should be avoided.

Evening colic (*Infantile colic, three-month colic*) is well-recognized entity of unknown etiology, characterized by unexplained crying spells in infants below 3–4 months of age during evenings with flexion of thighs and flushing of face. Each spell lasts for 2–3 hours and recurs with consistent regularity for many evenings (>3 days a week), before gradual cessation by 3–4 months of age.

Incidence: Infantile colic of variable severity is reported in ~5–20% of infants, more common in first-born, active babies of anxious parents.

Etiology is uncertain, probably related to aerophagia and intestinal colic, as evident from gurgling sounds and increased peristaltic movements in some cases. Crying further aggravates aerophagia, to form *colic-cry-colic* cycle.

Diagnosis depends on exclusion of other causes and typical presentation with regular periodicity and timing of spells, in an otherwise healthy and well-fed child.

Management includes—(a) reassurance to parents about benign nature of the problem, (b) training them to comfort the baby by rocking, cuddling and burping during the spell, and (c) counseling the mother about the proper feeding position and burping after feeds, anti-spasmodic drops and probiotics might be useful in some cases, though should preferably be avoided.

4.2 EATING DISORDERS

Minor feeding problems, e.g. refusal to eat, slow-feeding, picky-eating, spitting while feeding, etc. are common in infants and young children, reported by ~25–40% parents. Most of them are transient, self-limiting and are of little consequence, if the child is developing and growing normally. No intervention is required in these cases, except reassurance and guidance to parents.

Some common behavioral feeding problems in early childhood are discussed here, while others like anorexia nervosa and bulimia are largely seen in adolescents and discussed elsewhere (Ch 13.3).

4.2.1 PICKY-EATING

Picky-eating (Fussy, Faddy or Choosy-eating) is a common behavior in early childhood but may cause considerable stress to parents. It is characterized by an *unwillingness to eat familiar foods or to try new foods, as well as strong food preferences*.

Incidence: Estimated prevalence of picky-eaters varies widely from 5–50% of infants, due to lack of consistency in definition or assessment. Incidence gradually starts increasing from 18–24 months of age and peaks at ~5–6 years, before declining. Picky-eating is more common in single children of young-inexperienced parents.

Etiology is uncertain, but factors like delayed or inappropriate introduction of complimentary feeding, forced feeding, choosy dietary habits of the family itself and babies' own personality trait seem to be important among picky-eaters. Maternal eating behavior and food preferences have been also suggested to influence child's food habits.

Consequences: While energy intake in picky-eaters is usually adequate, these children are at-risk for undernutrition due to poor dietary diversity and micronutrient deficiencies. Constipation is common and some may develop serious behavioral problems, e.g. anorexia nervosa, in later life.

Some picky-eaters are also at rare risk to develop *Avoidant/restrictive food intake disorder (ARFID)*, a serious mental health problem in older children or adolescents, characterized by the overall lack of interest in food and/or aversion to eat large number of foods. Aversion may be due to the appearance, smell, taste, etc. or due to fear of adverse consequences based on past experiences, e.g. retching, vomiting or gagging, etc.

Management involves reassurance to parents, avoidance of force-feeding, encouragement or rewards to improve dietary diversity (positive reinforcement) and assessment for underlying behavioral problems in child as well as in family.

4.2.2 PICA

Pica, i.e. *perverted appetite*, is the commonest eating disorder, defined as *"a pattern of eating non-nutritive non-food substances for–(a) at least one month (b) inappropriate to the child's developmental level, and (c) not a part of culturally supported or socially normative practice" (DSM V criteria).*

Substances commonly ingested in pica are clay, dirt and mud (geophagia); paint, pencil-lead (plumbophagia), ice (pagophagia), starch (amylophagia), feces (coprophagia), hair (trichophagia), plaster, ash, wool/cloth, leaves, coal, soap, etc.

Incidence: Pica is a normal developmental behavior till 24 months of age, as infants have a tendency to mouth all objects grasped by their hands. Persistence of pica beyond this age is abnormal, estimated to be present in ~20–30% in toddlers and ~10% in older children. Incidence is relatively higher in low-socioeconomic status, similar family history and institutionalized children.

Etiology: While Pica is largely a behavioral disorder, it has been associated with: (a) mental retardation, (b) emotional neglect, (c) iron and zinc deficiency, and (d) worm infestations (? cause?? effect).

Complications: Children with pica are at risk for: (a) GIT problems, e.g. recurrent abdominal pain, diarrhea or worm infestation, (b) chronic lead poisoning and (c) iron deficiency anemia. Rarely, these cases may develop bezoars, intestinal obstruction or perforation.

Diagnosis is clinical, though investigations, e.g. hemogram (for anemia and infections) and stool examination (for worm infestations) are indicated in all cases. Serum lead estimation may be required in relevant cases.

D/D of pica includes more serious psychological disorders, e.g. autism, schizophrenia, and physical disorders, e.g. Kline-Levine syndrome.

Management of pica includes:

a. *Treatment of predisposing/complicating factors*, e.g. iron deficiency anemia, helminthiasis and lead poisoning;
b. *Parental counseling* regarding –(i) benign and self-limiting nature of problem, (ii) need to provide emotionally stimulating environment to the child and (iii) supervision to keep potentially dangerous substances out of the reach of child;
c. *Behavioral modification* strategies, e.g. positive reinforcement, occasional negative reinforcement or mild aversion therapy.

Rumination is a rare but severe vegetative disorder in infants (3–12 months), characterized by *self-induced or spontaneous regurgitation of food* after feeding (akin to anorexia nervosa/bulimia in adolescents). It is more common in males and emotionally deprived children, often leading to severe failure to thrive and occasionally death.

Severe feeding disorders of infancy or early childhood are defined as *persistent feeding disturbance with: (a) failure to gain weight or significant weight loss for at least one month, (b) no significant medical conditions, mental disorder or lack of available food*, and (c) *age of onset less than 6 years* (DSM-IV criteria).

Incidence: Severe feeding disorders are seen in only ~1–2% of under-five children, more common in those born prematurely or having some developmental handicap.

Types: These disorders are classified in many ways, usually into six sub-types: (a) *feeding disorder of state regulation*-difficulty to maintain a calm state during feeding, e.g. too sleepy or agitated, (b) *feeding disorder of social reciprocity*-no appropriate response to the care-giver while feeding, e.g. smiling or babbling, (c) *infantile anorexia*-lack of interest or refusal to eat adequate amounts of food for at least 1 month below 3 years of age, (d) *sensory food aversions*-refusal to eat foods with specific tastes, textures, or smell, (e) *feeding disorder associated with concurrent medical condition*, e.g. cleft-palate, *and* (f) *feeding disorder associated with previous insults* to the gastrointestinal tract, e.g. choking, severe vomiting, suction, intubation, etc.

Management of these serious feeding disorders requires detailed clinical and behavioral assessment, relevant investigations and a team-approach in management, which is beyond the scope of this book.

4.3 ELIMINATION DISORDERS

An infant is expected to achieve developmentally appropriate bowel control by ~18 months, bladder control by ~24 months during day-time and ~36 months during nights. Elimination disorders include problems related to these vegetative functions, e.g. enuresis and encopresis.

4.3.1 ENURESIS

Enuresis is the commonest elimination disorder, characterized by repeated involuntary passage of urine, beyond the normal age of bladder-control, i.e. ~24 months during day-time and ~36 months during nights. However, occasional bed wetting is not uncommon till 9–10 years.

Depending on the time of occurrence, enuresis is termed as nocturnal (only during sleep) or mixed (nocturnal as well as diurnal). Isolated diurnal enuresis is extremely rare.

As per DSM V criteria, enuresis is defined as "*repeated involuntary or intentional voiding of urine into bed/clothes beyond 5 years of age*, with:

a. Frequency of at least twice a week for at least 3 consecutive months, *or*

b. Presence of significant emotional distress *or* social or academic impairment, and
c. *Without* being the effect of a substance, drug or medical condition, e.g. urinary tract infection.

Incidence of enuresis varies with age, estimated to be ~3–7% at five years and ~2–3% at ten years, being more common in boys.

Etiology: Enuresis may be *primary*, in which the child has never achieved bladder control or *secondary*, in which the enuresis has re-started after a dry period of at least ≥ 6 month. Over 75% cases on enuresis are primary.

Primary enuresis is mostly functional, due to delayed maturation in bladder functions. It is more common in boys (3:1) with similar family history. Various factors attributed in causation of primary enuresis include: (a) premature and/or coercive attempts for toilet-training, (b) abnormal sleep-awake cycle, (c) lack of normal nocturnal surge in ADH secretion, (d) inadequate bladder capacity (e) mental sub-normality, and (f) emotional deprivation. Organic primary enuresis is rare (<5%), seen in cases with neural tube defects or congenital urinary tract malformations.

Secondary enuresis is usually due to *recent emotional stress* in family or school, e.g. birth of a sibling, change in school, etc., or more likely due to an underlying organic pathology. Important organic causes for secondary enuresis include: (a) urinary tract infections, (b) obstructive uropathy, (c) diabetes mellitus or diabetes insipidus, (d) neurogenic bladder, and (e) seizure disorders. Involuntary passage of urine may be the only indicator of unobserved seizure at night.

Diagnostic evaluation of these cases includes:

- *Detailed history*, specially related to age of onset (primary vs. secondary), the time of enuresis (nocturnal, mixed), similar family history, co-existing problems, e.g. dysuria, encopresis, general development and behavioral profile of the child as well as family.
- *Physical examination* to exclude organic etiology, including palpation for enlarged kidneys or full bladder, examination of external genitals and urinary stream, spinal examination for spina-bifida and detailed neurological evaluation.
- *Investigations should* begin with routine urine analysis and culture to exclude urinary tract infection, followed by other relevant tests, e.g. renal function tests, spinal X-rays, urinary tract imaging and urodynamic studies.

Management needs to be individualized in each case, depending on suspected causative or precipitating factor. Organic causes, though rare, should be looked for and treated. Broad recommendations for behavioral management include:

a. *Parental and child counseling*, regarding the nature, probable cause, correct approach towards toilet training and expected results of therapeutic interventions.
b. *Bladder stretching exercises*, e.g. voluntary holding the urine as long as possible in daytime to increase bladder capacity and repeatedly starting/stopping of stream during micturation to increase the sphincter tone.
c. *Habit modifications*, e.g. early dinner (4 hours before sleep), restricted fluid intake after dinner, voiding before retiring, waking the child at night to pass urine, etc.
d. *Behavioral modification* with positive reinforcement, i.e. rewards for dry nights. Negative conditioning, e.g. punishment or humiliation of the child should be strongly discouraged. Psychotherapy, e.g. play-therapy and hypnosis may be used in some cases.
e. *Conditioning devices*, e.g. bed-wetting alarms are useful in refractory cases, with success rate of >70%. In these devices, a sensor attached to the child's underwear or mattress is stimulated as soon as she/he wets the bed, completing an electronic circuit to buzz the alarm and wake the child.
f. *Pharmacotherapy*, should be reserved for selected cases of above 5 years of age and non-responsive to behavioral modification.
   - *Desmopressin acetate* (PO 0.2 mg single dose ~2 hours before bedtime, maximum 0.6 mg/dose) is the drug of choice for enuresis, with success rate of >50%. Treatment should continue for at least 4–6 months (or >4 weeks of consecutive dry nights) to minimize relapse, which may occur in ~70% cases. Desmopressin nasal spray are no longer recommended due to potential but rare risk of hyponatremia and seizures.
   - For resistant enuresis, anticholinergic therapy with PO *Oxybutynin* 5 mg or PO *Tolterodine* 2 mg may be used in combination with desmopressin to reduce uninhibited bladder contractions, specially in children with urge incontinence during daytime. Constipation is a potential side-effect.
   - *Imipramine* (PO 1–2 mg/kg single dose ~2 hours before bedtime), a tricyclic antidepressant to alter arousal-sleep cycle, is rarely used nowadays due to higher relapse rate (90%) and side-effects, e.g. dry mouth, irritability, insomnia and urinary retention.

Giggling incontinence is an uncommon problem in otherwise continent children, characterized by sudden, involuntary, uncontrollable passage of urine during giggling or laughing heartily. It is more common in girls. While most children overgrow this problem, urodynamic studies are warranted in some cases to exclude organic problems.

4.3.2 ENCOPRESIS

Encopresis, i.e. involuntary or intentional passage of feces in inappropriate places beyond the normal age of control, is less common than enuresis.

As per DSM V criteria, encopresis is defined as:

a. frequency of at least once a month for minimum 3 months,
b. persistence beyond 4 years of age, and
c. not due to a substance, drug or medical disorder.

Encopresis may be *Primary*, when toilet training was never achieved or *Secondary* (Regressive) when it reappears in previously continent children for over one year.

Incidence: Encopresis is more common in boys, with an estimated incidence of ~1% at 5 years of age.

Etiology: Encopresis may be classified as retentive or non-retentive.

- *Retentive encopresis* is usually due to chronic constipation with overflow incontinence, e.g. Hirschsprung's disease, anal fissures, hypothyroidism, substance (opiates) abuse and habitual use of laxatives.
- *Non-retentive encopresis* without evidence of fecal retention indicates serious emotional disturbance, often associated with suppressed anger and defiance to coercive toilet training, sexual abuse and negative defecation experiences.

Diagnostic evaluation includes: (a) detailed psychosocial history, (b) per-rectal examination and neurologic evaluation to exclude organic causes, and (c) relevant investigations, e.g. thyroid function tests, anal manometry and barium studies for congenital or acquired megacolon.

Management includes: (a) initial *treatment of constipation* with laxatives, stool-softeners or enema, (b) *prevention of further constipation* by high-fiber diet, (c) *voluntary toilet training to* encourage the child to visit the toilet 10–15 minutes after each meal to induce gastrocolic reflex, (d) *behavioral modification* i.e. positive reinforcement (rewards) for better bowel control, and (e) *psychotherapy* for precipitating and secondary psychological events.

Prognosis: Encopresis is more difficult to control than enuresis and secondary psychological problems are common, e.g. loss of self-esteem, sense of guilt/ depression and frequent school absenteeism.

4.4 HABIT DISORDERS

All children have one or more habits, i.e. repetitive pattern of movements, at some point of time. The term *habit disorder denotes unusual persistence of some habit/s, which interfere in their physical, emotional and social functioning.* Most of these disorders indicate a physical expression of underlying emotional tension (tension-discharge phenomena).

While the list of habit disorders is endless, e.g. head nodding/ banging, body rocking, eye-blinking, throat-clearing, body manipulations, some important ones are discussed here.

Bruxism is one of the commonest habit disorder, characterized by *non-functional repeated grinding of teeth* with a high-pitched sound, usually during sleep. Nocturnal bruxism occurs in ~15% children at some time during childhood.

Etiology: Bruxism is usually considered as a *tension-discharge activity* for the suppressed anger, resentment or anxiety. However, some cases may be associated with: (a) abnormal sleep activity, (b) familial behavior pattern, (c) anal pruritus, e.g. pinworm infestation, and (d) neurological diseases, e.g. mental retardation or cerebral palsy. No relationship with the dream sequence is established.

Management: Bruxism usually subsides spontaneously over time. However, severe cases need: (a) *detailed behavioral evaluation* for underlying psychological conflicts, (b) *behavioral modification* via positive reinforcement (rewards), and (c) *parental counseling* regarding the need for open communication with child. *Psychotherapy, e.g.* hypnosis and pharmacotherapy, e.g. diazepam is very rarely required.

Thumb-sucking is a common habit among infants and toddlers and most children overgrow it by 3–4 years. Persistence of this habit beyond this age is abnormal.

Etiology: Thumb sucking is usually considered as an indicator of *insecurity* and *anxiety*, often associated with (a) emotional neglect, (b) over-disciplined or over-protective rearing, and (c) inherently shy or stubborn behavior.

Clinically, apart from hygiene issues, prolonged thumb-sucking may lead to significant adverse effects, e.g. (a) dental problems, e.g. malocclusion, periodontitis, (b) nail deformities, e.g. chronic paronychia, (c) speech problems, and (d) recurrent diarrhea or worm infestations.

Management: No intervention is required till 4 years of age, except parental counseling. Forcible and over-enthusiastic efforts generate hostility in the child and perpetuation of this habit for a longer time.

In older children, important steps of management include: (a) *psychosocial evaluation and counseling* regarding appropriate parent-child relationship, (b) *behavioral modification* with positive reinforcement, e.g. praising the child's efforts to discard this habit, (c) *distractions,* e.g. engaging him into other activities at the time of habit activity, and (d) *treatment of physical complications*. Application of bitter substances over thumb/fingers or physical restraints, e.g. splinting of hands, may be useful in some cases, though should be avoided.

Nail-biting (Onychophagia) is a common habit in relatively older children, reported in ~30% of school children and even adolescents.

Etiology: Nail-biting too, like thumb-sucking, usually reflects suppressed *anxiety* and is relatively common in children who had thumb-sucking in early childhood. It is also a tension-discharge behavior, which sometimes borders as compulsion or overlapping obsessive-compulsive disorder. Precipitating factors include emotional stress, lack of self-confidence and self-esteem. Co-morbidities, e.g. enuresis, intellectual disability and attention-deficit hyperactivity disorder are common.

Clinically, nail-biting as base-line habit, is often aggravated during the periods of stress. In long-term, it may lead to acute/chronic paronychia, bleeding and permanent damage/deformities to nails. Recurrent diarrhea and worm infestations, e.g. enterobiasis and dental problems are also common.

Management includes: (a) *emotional support during stressful situations* to build the self-confidence of child, (b) *behavioral modification* with positive reinforcement, e.g. praising the child's efforts to discard this habit, (c) *distractions*, e.g. engaging him in other activities at the time of nail-biting, and (d) *treatment of physical complications*.

Tics are characterized by *involuntary, sudden, rapid, recurrent, non-rhythmic or stereotyped motor movements or vocalizations.* Tics are more common in school children, though also seen in children as young as 2 years.

Etiology: Tics are usually benign *tension-discharge* activities, although occasionally seen in psychiatric syndromes, perinatal problems, chorea or encephalitis.

Clinical presentation: Broadly, Tics may be classified as motor or vocal and simple or complex.

- *Simple motor tics* are repetitive, rapid contractions of functionally similar muscle groups, e.g. eye-blinking, lip-smacking, grimacing, body rocking, head banging, etc.
- *Complex motor tics* are less common and involve more purposeful and ritualistic behaviors, e.g. grooming behaviors, smelling/touching of objects, echopraxia (imitation) and copropraxia (obscene gestures), etc.
- *Complex vocal tics* include repeated use of words/phrases out of context, use of obscene words/phrases, Palilalia (repetition of one's own words), and Echolalia (repetition of last words, heard from others).

Generally, tics tend to worsen with emotional stress or parental attention and relieved on distraction or sleep. Multiple tics may be present in the same child or one tick may change to another after some time.

Diagnosis: Tics need to be differentiated from *partial seizures* and d*yskinetic/dystonic extrapyramidal disorders,* on the basis of: (a) changing frequency during stress and sleep, (b) amenability for voluntary control, and (c) normal EEG.

Tics need to be differentiated from ***stereotypies***, which are classically rhythmic, distractable and persist for long time.

Management: Although no specific management is required for benign ticks, socially distressing habits may require: (a) *parental counseling* to ignore the symptom, (b) *behavioral modification* with positive reinforcement, and rarely, (c) *drugs,* e.g. haloperidol in resistant tics.

Gilles *De La* Tourette syndrome is a rare but severe tick disorder, characterized by a *motor component,* e.g. multiple tics and a *vocal component,* e.g. compulsive barking, grunting or shouting obscene words (Coprolalia). It is more common in boys (3–4:1) and first-degree relatives of similar cases.

Etiology: Exact etiology is uncertain, though many factors, e.g.: (a) genetic defect, (b) neurobiological abnormality, (c) emotional and environmental stress, (d) dopaminergic drugs and (e) a pediatric autoimmune neuropsychiatric disorder secondary to streptococcal infection (PANDAS), have been implicated as causative or precipitating events.

Clinical features: Full-blown *Gilles de la Tourette* syndrome is relatively rare in children than in adults. Usually, the motor component appears by ~7 years of age and almost always precedes the vocal component. Early disorder with only motor component is difficult to distinguish from simple tics, though behavioral, emotional and academic problems are more common in this syndrome.

Diagnosis is largely clinical with no specific diagnostic tests. EEG shows non-specific abnormalities in ~80% cases. Verbal scores on psychometric testing are usually low.

Management includes: (a) *parental counseling* regarding the compulsive nature of behavior, (b) *behavior therapy* with positive reinforcement and c) *pharmacotherapy* with a dopamine antagonist, e.g. haloperidol or pimozide, which may reduce the severity of tics by >50%. Other drugs, e.g. clonidine, clonazepam and carbamazepine have been also used.

Prognosis: *Gellis de la Tourette* syndrome persists throughout life, though usually with a considerable reduction in symptoms after 10–15 yrs of initial diagnosis.

Stuttering or stammering is a fluency disorder of speech characterized by difficulty in initiation of some consonants, spasmodic repetition of sounds or syllables or words and pauses or interruptions in speech, known as blocks. Stuttering is common in 2–5 years of age during the phase of rapid language development and resolves spontaneously with advancing age. However, ~1% older children continue to have significant stammering, especially during stress.

Clinically, stuttering denotes unusual hesitancy to speak during the stress or excitement, aggravated when the

child is reminded or corrected while stammering. It is often absent in low-stress settings like playing alone or singing. Many cases develop secondary mannerisms, e.g. blinking of eyes or twitching of facial muscles during speaking, as well as social anxiety and low-self-esteem, avoiding social interactions.

Management includes: (a) reassurance to parents about self-regressing nature of stuttering with age, (b) avoidance of teasing or scolding the young child while stuttering, (c) encouraging loud-reading or speaking in low-stress situations without undue attention, (d) emotional support to anxious child, and (e) *speech therapy* in older children, if the problem persists. Cognitive behavior therapy may be useful in children with major behavioral issues. Drugs like haloperidol or clonidine may be considered in rare cases of socially or functionally debilitating tics.

Masturbation, i.e. stimulation of one's own genitals to derive the pleasure (also termed as gratification disorder), is common even in preschool children. About 30% of boys and 10% of girls are reported to engage in masturbation by 8 years of age, with incidence increasing to >90% by adolescence.

Masturabation is usually a benign habit, sometimes triggered by emotional disturbances, e.g. boredom, agitation or even systemic problems, e.g. abdominal pain or urethral/vaginal irritation. However, compulsive masturbation that interrupts normal activities, engage public displays or lead to development of anxiety or self-guilt, needs intervention.

Management involves reassurance about harmless nature of activity, counseling to avoid such acts in public and maintenance of hygiene, parental education and behavior therapy by experts. Medications are of very limited benefit in these cases.

4.5 SLEEP DISORDERS

Sleep pattern of a child depends on the age, behavioral pattern, frequency/duration of daytime naps and environment during bedtime. A newborn sleeps for >20 hours/day, which is gradually reduced to 8 hours by the end of first year. Circadian rhythm, i.e. day-night pattern of sleep, begins to establish by 3 months and is well established by ~18–24 months.

Biological temperament and emotional stress, e.g. separation anxiety, home/school fears, insecurity, etc. are most important causes of sleep problems in childhood, though *important organic causes* include (a) obstructive sleep apnea syndrome, (b) organic brain disorders, e.g. attention-deficit disorder or autism, (c) other, e.g. Prader-Willi syndrome.

Common sleep disorders include: (a) insomnia or interrupted sleep, (b) hypersomnia or narcolepsy, and (c) parasomnias, e.g. somnambulism (sleep-walking), nightmares or night terrors.

Parasomnia refer to abnormal behavior or motor manifestations during sleep and include:

- Parasomnias during early NREM sleep, presenting with sleep walking (awake and ambulatory), confusional arousals (awake but not ambulatory) and night terrors.
- Parasomnias during late REM sleep include night mares and bizarre movements/behavior.

All these conditions are self-limiting and no specific treatment is required except reassurance.

Night-terrors are commonest sleep problems in pre-school children, characterized by sudden arousal from sleep in disoriented state with screaming and signs of intense autonomic activity, e.g. labored breathing, tachycardia, sweating and dilated pupils. Some children may sleep-walk (somnambulism) for few minutes, before getting oriented or going back to sleep. History of a bad dream (nightmare) is often present. Though occasional attacks are common, recurrent night terrors indicate significant underlying phobia, anxiety or emotional trauma.

Narcolepsy is rare, characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations and poor school performance.

It is also considered as a paroxysmal disorder or seizure mimics, with attacks of irrepressible sleep attacks during day time, from which the patient is easily arousable (d/d absence seizures). EEG reveals intermittent attacks of REM sleep. Modafinil acetamide (PO 200 mg OD) is drug of choice in confirmed cases.

4.6 CONDUCT DISORDERS

Children are expected to behave within socially acceptable limits, determined by their age, social norms, training/moral standards and parent-child relationship. *Negativism*, i.e. opposition to parental instructions is a normal phase of development during 18–36 months of age, leading to anger and frustration. By 4–5 years, children learn to control their behavior.

Conduct disorders (disruptive behavioral disorders) denote an anti-social behavior, usually due to parent-child conflict, child's urge for autonomy and expression of underlying anger, defiance or frustration. Emotional neglect and over-disciplined rearing are two important determinants of early disruptive behavior, apart from biological temperament, role models and social circumstances.

While many disruptive behaviors are seen in children, common ones are breath-holding spells and temper tantrums in under-five children and lying, stealing, truancy, etc. in older children. Serious disruptive behavior disorders, e.g. juvenile delinquency, substance abuse, teen pregnancy, etc. are more common in adolescents, discussed in Ch 13.3.

4.6.1 BREATH-HOLDING SPELLS

Breath-holding spells are commonest but benign manifestations of disruptive behavior in infants and toddlers, characterized by *'sudden holding of breath in expiration (apnea), leading to cyanosis or pallor with/without loss of consciousness, hypotonia and seizures'*. Frequency of these spells may vary from occasional attacks to >10–15 spells a day.

Incidence: Breath-holding spells are most common between 6 months to 2 years of age (up to 6 years), during which ~4–5% children experience at least one of these spells. Other high-risk factors include male sex, similar family history and labile temperament.

Etiology: Breath-holding spells are means of expression in a baby for internal frustration, anger and aggression. However, these episodes are essentially involuntary in nature, also termed as non-epileptic paroxysmal disorders.

Clinically: There are two major types of breath-holding spells; the more common *cyanotic spells* and the less common *pallid spells.*

- *Cyanotic breath-holding spells* are usually provoked by anger or frustration (akin to temper tantrum in older children), with a typical sequence of events - a loud shrill cry > forced expiration > breath-holding, i.e. apnea > cyanosis and unresponsiveness. Usually, each spell does not lasts for >10–15 seconds and terminates with a deep gasp > restarted breathing and > gradual disappearance of cyanosis. Baby may remain drowsy for a few minutes after the spell, before complete recovery. However, occasional attack may progress to develop generalized seizures, opisthotonus and bradycardia. *Interictal EEG is normal.*
- *Pallid breath-holding spells*, are less common and differ from cyanotic spells in following features: (a) usually provoked by sudden painful stimulus, e.g. fall, blunt injury or loud noise, (b) pallor and limpness instead of cyanosis, and (c) usually abnormal *interictal EEG.* Pallid spells may be induced by supraorbital pressure to stimulate oculocardiac reflex, though such maneuvers are risky and should be avoided.

Diagnosis depends on typical sequence of events, though should be differentiated from epilepsy, hypercyanotic (Tet) spells in cyanotic heart diseases and cardiac arrhythmias, e.g. long-QT syndrome (d/d pallid spells).

Prognosis: Except a rare prolonged spell with significant hypoxia, breath-holding spells are essentially benign and disappear by 5–6 years of age. However, these children tend to have higher incidence of behavior problems in later life, e.g. temper-tantrums or syncopal attacks.

Management aims towards behavioral modification of the child and for early abortion of the attack, and includes:

a. *Management during the attack:* These spells can be easily aborted by physical stimulation, e.g. pinching, shaking, supra-orbital pressure, blowing air or sprinking water on the face, for which parents must be trained. Other precautions during the spell include avoidance of injury and aspiration by placing the child in lateral position, if looses the consciousness.

b. *Parental counseling:* Parents need to be reassured about benign nature of these spells and the underlying behavioral basis. It is important to emphasize the need for certain discipline and consistency in childcare. The baby's demand, which has provoked the spell, should not be fulfilled immediately on recovery (purposeful neglect). Parents should also try to divert the attention of child from a potential precipitating event.

c. *Pharmacologic therapy*: Iron supplementation may be effective in some cases to reduce the frequency of attacks, even in absence of significant anemia. In children with pallid spells, recurrence of these attacks during a painful procedure may be prevented by previous atropinization.

4.6.2 TEMPER TANTRUMS

Temper tantrum are characterized by *physical aggression*, e.g. *crying, howling, kicking, head banging, throwing objects*, etc. in relatively older children above 2 years of age. Most of them learn to control their behavior by 5 years with gradual reduction in frequency of temper tantrums.

Incidence: Temper tantrums are common in children toddlers and pre-school children (~10%), with risk factors including over-indulgent child-rearing, e.g. in single child or working parents.

Etiologically, Negativism or defiant behavior is a normal phase of behavioral development in pre-school children, aimed to ascertain their autonomy. Temper tantrums are manifestations of excessive defiance and expression of internal anger and frustration. Parental anger and frustration may reinforce this defiance. Fatigue and hunger tend to trigger these attacks.

Management includes parental counseling regarding: *(a) prevention of injury* during the attack, *(b) firm and consistent attitude* towards the child, but with good communication, *(c) purposeful neglect* during attack, i.e. ignoring the child's demand till the behavior is controlled, *(d) positive reinforcement*, i.e. praising or awarding him for periods of controlled anger. Parent should remain calm and firm during these episodes and must try to distract the child from a potential precipitating event.

4.7 ANXIETY DISORDERS

Anxiety/fear is a normal part of development, beginning with stranger's anxiety/fear by 6–8 months of age. The term *anxiety disorders or neurosis* denotes *'disproportionately excessive anxiety to a real event or undue*

anxiety to an imaginary cause'. Common types of anxiety disorders include:

a. *Phobia,* e.g. school phobia (in ~1–2% children) or social phobia, i.e. fear to meet unfamiliar people;
b. *Obsessive-compulsive disorder,* i.e. repetitive thoughts, acts, rituals, e.g. compulsive hand washing, checking of locks, etc.;
c. *Specific anxiety disorders* including separation anxiety, i.e. unrealistic worry towards parents or fear of loneliness and post-traumatic stress disorder;
d. *Generalized anxiety disorders*, more common in adolescents with unrealistic worry for future events, e.g. academic failure.

Post-traumatic stress disorder (PTSD) is an anxiety disorder seen in all age groups including children, in response to any external event, experienced or witnessed by an individual and perceived as dangerous.

Etiology: Life-threatening situations leading to serious injuries or death, e.g. riots, natural disasters, etc. are frequently associated with PTSD. Younger children, females and individuals with high-anxiety personality trait are at an increased risk of PTSD. Physical/sexual abuse is an important cause of PTSD in children.

Incidence of PTSD depends on the severity of precipitating event. Although only ~1% of exposed adults satisfy the DSM criteria for PTSD, over 15% are estimated to suffer with more non-specific stress behavior for a variable period of time. Children are more vulnerable for PTSD than adults.

Clinical features: PTSD may be acute or chronic.

Acute PTSD is characterized by: (a) recurrent recollections and dreams of the traumatic event, (b) intense anxiety, (c) sleep disturbances with startle reactions, and (d) concentration difficulties.

Chronic PTSD is generally seen in children with prolonged physical/sexual abuse, leading to changes in the attitude towards life, people, future, etc., psychologic numbing, i.e. forced amnesia and isolated life-style.

Management: Early identification and management of PTSD is essential to prevent long-term psychotic morbidity and includes:

- *Initial evaluation* to explore the child's understanding, vulnerability and reactions to the traumatic event.
- *Psychotherapy* to provide the child an opportunity to discuss the event and express his/her feelings of helplessness, sadness or anger. She/he should be helped to understand everyday events and distinguish them from past-trauma.
- *Family therapy and parental counseling* to make them understand the basis of child's behavior and encourage their participation in day-to-day management.
- *Pharmacotherapy* with drugs, e.g. *benzodiazepines* to modify the sleep and arousal behavior, in selected cases.

Stranger anxiety is a normal phase of development to appear at ~6 months and lasts till 15–18 months. During this phase, infants tend to avoid interaction with unfamiliar persons and cry or move away from them, towards the parents. No treatment is required except reassurance to parents and emotional support to the child. However, unusually intense discomfort with excessive crying, psychological distress or persistence of this phase beyond second year of life may be an indication of serious behavioral problem, e.g. separation anxiety disorder. Such cases need psychiatric referral for complete evaluation and interventions, e.g. cognitive behavior therapy.

4.8 PSYCHOSOMATIC DISORDERS

Although emotional stress is a known precipitating/exacerbating event for many medical illnesses, e.g. asthma, diarrhea or epilepsy; two specific and important psychosomatic illnesses are conversion disorder and Munchausen syndrome by proxy, discussed here.

Conversion Disorder: The term conversion disorder denotes loss or alteration of physical functioning without a demonstrable illness. This disorder is usually seen in adolescents and older children and more common in females.

Etiologically, it is considered as a physical medium of expression (somatization) of suppressed anger or frustration, especially in over-disciplined children.

Clinically, these cases may present with:

a. Conversion reactions with motor component (hysteria), e.g. mimicked seizures, paralysis, blindness, etc. or rarely,
b. Dissociative reactions, e.g. recurrent abdominal pain, vague body aches and pains, anorexia, etc.

Diagnosis usually rests on exclusion of organic cause, absence or inconsistency of clinical signs, and prolonged observation of behavior. Conversion reactions tend to increase during family/doctor's attention, though frequently, these responses are not within the patient's voluntary control (d/d Factitious illnesses).

Treatment is non-specific during acute phase except exclusion of organic/concomitant illnesses, while psychotherapy is necessary on recovery to prevent recurrence.

Munchausen by proxy syndrome is a form of child abuse; characterized by *illnesses fabricated in children by their parents*, usually mother, in order to get medical attention. These babies are repeated brought for medical consultations with non-existing illnesses, multitude of complaints or problems induced by parents themselves, e.g. bruises, hematuria, fever, vomiting, etc. and some parents even alter the laboratory samples or

temperature measurements of the child to substantiate their complaints.

Important ecological factors include disturbed family, mentally unstable mother or unwanted child.

Clinically, these children present with large spectrum of unexplained symptoms, e.g. fever, vomiting, diarrhea, seizures, hematuria, etc.

Diagnostic indicators include: (a) exotic and wide-spectrum of complaints, (b) discordant physical examination, (c) extremely anxious or unconcerned mothe, (d) history of multiple medical consultations (Doctor shopping), (e) poor response to rational therapy, and (f) absence of symptoms on separation from parents.

4.9 CHILD GUIDANCE CLINIC

Child guidance clinic (CGC) is a specialized health service, based on an *integrated and multidisciplinary approach* to deal with the behavioral and developmental problems of children and adolescents, who are not fully adjusted to their environment. The first child guidance clinic was started in Chicago in 1909.

Objectives: CGCs aim: (a) to identify children with developmental and behavioral problems, (b) to provide comprehensive management for these problems with a teach-approach, (c) to provide appropriate guidance, counseling and support to the parents and family, and (d) to refer children who need specialized services, if required.

Target problems: Individual problems attended in CGC usually include developmental delay, learning disorders, habit disorders, personality disorder, psychosomatic disorders, antisocial behavior and established psychiatric disorders, e.g. autism and attention deficit-hyperactivity disorders (ADHD).

Approach: Child guidance is a team-work comprising of psychiatrist, clinical psychologist, educational psychologist, psychiatric social worker, pediatrician, public health nurses, speech therapist, occupational therapist and a neurologist. The psychiatrist is the most important member of the team who, with others, arrives at a diagnosis and formulates the management plan.

Pediatrician is usually the first contact point for children with behavioral problems and his/her role is crucial in identification of problem, exclusion and treatment of physical causes and timely referral to the child guidance clinic.

Activities: Important functions of CGC include: (a) evaluation of new cases, (b) follow-up of old cases, (c) behavioral interventions including group therapy, play therapy and psychotherapy, (d) parental counseling and support for home management, (e) training and research in the field of behavioral and developmental disorders.

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CHAPTER

5

Normal Nutrition

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Nutrition is a dynamic process to supply adequate nourishment for survival, growth and development, repair and creation of future reserves. Weight-wise, nutritional requirements of children are relatively higher than in adults due to higher basal metabolic rate, active growth, building of stores and more pronounced physical activity.

5.1 BASIC CONSIDERATIONS

Diet is the main source of nutrition in children, though some nutrients, i.e. vitamin D and K are also synthesized endogenously in body. An ideal diet should fulfil requirements of all essential nutrients in adequate proportions and composition.

5.1.1 NUTRITIONAL REQUIREMENTS

Often used interchangeably, the term *Nutritional requirements* refers to daily physiological requirements of various nutrients to maintain normal metabolism, while the term *Dietary requirements* denote *need for* daily nutritional intake, essential to fulfil these nutritional requirements after considering absorption and other losses.

Recommended dietary allowances (RDA) is defined as the *'minimum daily dietary requirement of a nutrient in normal healthy person along with some additional allowance for individual variations to cover the needs for >97.5% of healthy (not sick) population, without the risk of over-dosage'*. National Institute of Nutrition under Indian Council of Medical Research (NIN-ICMR) has periodically revised RDA for various nutrients for Indian population, with latest recommendations in 2020 **(Table 5.1)**.

However, there is no specific RDA for energy in 2020 version, instead provided as "Estimated Average Requirement" (EAR), i.e. median daily intake, estimated to meet requirements of half of the healthy individuals in different age/sex groups.

TABLE 5.1 : Recommended dietary allowances* (RDA) for Indian children and adults

Age	*Calories* (Kcal/d)*	*Proteins (g/d)*	*Vit. A (µg/d)*	*Vit. C (mg/d)*	*Vit. D (IU/d)*	*Iron (mg/d)*	*Calcium (mg/d)*	*Iodine (µg/d)*	*Zinc (mg/d)*
0–6 months	530	8.0	350	20	400	-	300	100	-
6–12 months	680	10.5		30		3		130	2.5
1–3 years	1110	12.5	390		600	8	500	90	3.3
4–6 years	1360	16	510	35		11	550		4.5
7–9 years	1700	23	630	45		15	650		5.9
10–12 years	2220 (2060)	32 (33)	770 (790)	55 (50)		16 (28)	850	100	8.5
13–15 years	2860 (2400)	45 (43)	930 (890)	70 (65)		22 (30)	1000	140	14.3 (12.8)
16–17 years	3320 (2500)	55 (46)	1000 (860)	85 (70)		26 (32)	1050	140	17.6 (14.2)
Adults**	2710 (2130)	54 (46)	1000 (840)	80 (65)		19 (29)	1000	140	17.0 (13.2)
Pregnancy	+350	+9.5/+22[1]	900	+15		27	1000	220	14.5
Lactation	+600	+17/+13[2]	950	+50		23	1200	280	14.1

*Denote Estimated Energy requirements for calories instead of RDA, **Moderate worker
[1]In second and third trimester of pregnancy, [2]in first 6 months and during 6–12 months of lactation
Figures in parentheses represent RDA in females, wherever different from males.
Source: Dietary Guidelines for Indians, National Institute of Nutrition, Hyderabad, 2020.

TABLE 5.2: Normal energy requirements (Holiday and Segar formula)

Body weight	*Energy requirements*
<10 kg	100 cal/kg
10–20 kg	1000 cal + 50 cal/kg above 10 kg
>20 kg	1500 cal + 20 cal/kg above 20 kg

Energy is the prime essence of nutrition, required to sustain basal metabolic rate, day-to-day physical activity, normal growth, and to digest and assimilate the nutrients. *Basal metabolic rate* (BMR), e.g. the minimum energy requirement to maintain essential physiological functions of the body at rest, is highest in infancy (55 cal/kg/day) and decreases gradually with advancing age to reach adult values (25–30 cal/kg/day) by late childhood.

A normal child spends ~50% of energy requirements for BMR, 25% for physical activity, 12% for growth, 5% for digestion/assimilation of food and 8% for fecal losses.

Sources: Carbohydrates are the main source of energy in diet. An ideal diet should provide 50–60% of calories as carbohydrates, 20–30% as fats and 10–15% as proteins. *Each gram of proteins, fats and carbohydrates in diet provide 4, 9 and 4 calories, respectively.*

Requirements: Energy requirements in normal children vary according to the age and gender, provided as EAR in **Table 5.1**. For simplicity, these requirements may also be calculated with body weight by *Holiday and Segar formula* **(Table 5.2)**.

It should be noted that these are the requirements for normal and not the malnourished children, who need higher calories for catch-up growth and replacement of stores.

5.1.2 ESSENTIAL NUTRIENTS

Nutrients are the active principles in diet, each with different functions and metabolic patterns. These may be classified as:

- *Macronutrients or proximate principles*, e.g. proteins, fats and carbohydrates.
- *Micronutrients*, e.g. vitamins and minerals.

Proteins, which constitute ~20% of body weight, are important source of energy as well as required for: (a) body building, e.g. growth of muscles and different tissues, (b) repair and maintenance of tissues, (c) synthesis of substances, e.g. antibodies, plasma proteins, enzymes, hormones, hemoglobin, clotting factors, etc. (d) maintenance of osmotic pressure in various tissue compartments.

Biochemistry: Proteins are complex nitrogenous compounds made up of smaller units, e.g. *amino acids*. While some amino acids can be synthesized in body, others cannot and have to be essentially supplied from diet, termed as *essential amino acids*. In general, there are eight essential amino acids—*methionine, threonine, tryptophan, valine, isoleucine, leucine, phenylalanine and lysine* (acronym-MeTTVILPLy). Some other amino acids are essential only in infants (*histidine*) or low birth weight babies (*arginine, cysteine and taurine*).

Requirements: RDA for proteins in different age groups is given in **Table 5.1**. Protein requirements are relatively higher in PEM and during recovery from illnesses/infections, due to endogenous protein breakdown in muscles and liver to provide essential amino acids.

Sources: Dietary proteins are provided from *animal sources*, e.g. milk, meat, egg, fish, etc. as well as *vegetable sources*, e.g. cereals, pulses, beans and nuts. Quality of proteins from different sources differ, depending on the digestibility, biological value (% of absorbed proteins retained in the body) and net protein utilization or NPU (% of ingested proteins, retained in the body).

Animal proteins are nutritionally superior to vegetable proteins. *Egg is considered as a reference protein* due to its high biological value, digestibility and NPU (96%). NPU of other animal proteins is also relatively higher (cow's milk 85%, meat 76%, fish 74%) *vs* of vegetable proteins (rice 77%, wheat 61%). *Soya bean* is the richest source of vegetable protein but with lower NPU (<60%) due to poor digestibility.

Vegetable proteins also lack in certain essential amino acids, termed *'limiting amino acids'*. *Cereal proteins are deficient in lysine and threonine, while pulses are deficient in methionine.* Deficiency of limiting amino acids in vegetarian diet may be corrected by using combination of cereals and pulses in diet, e.g. rice-dal or dal-chapati.

Fats are the major source of stored energy (adipose tissue or brown fat) as well as also required: (a) as a vehicle for fat soluble vitamins, (b) as a source of essential fatty acids (c) for temperature regulation and (d) to increase palatability of food. Being the most concentrated source of energy (9 cal/kg), fats are commonly used to increase the caloric content of food without increasing its bulk.

Biochemistry: Fats are classified as *simple fats*, e.g. triglycerides, *derived lipids*, e.g. cholesterol, and *compound lipids*, e.g. phospholipids. Over 95% of dietary lipids and ~99% of stored lipids in diet are triglycerides.

Fats yield to fatty acids and glycerol on hydrolysis. Fatty acids may be classified as (a) *saturated* fatty acids, e.g. palmitic or stearic acid; *monounsaturated* fatty acids, e.g. oleic acid; and (b) *polyunsaturated* fatty acids (PUFA), e.g. linoleic acid, linolenic acid or arachidonic acid. Of these, PUFA cannot be adequately synthesized in body and have to be derived from ingested food, thus also termed *essential fatty acids* (EFA).

EFA are essential for: (a) normal growth and brain development, (b) structural integrity of cell membrane, and (c) inflammatory response to produce various mediators, e.g. prostaglandins. *EFA deficiency* has been linked with phrynoderma (dry skin), growth failure, developmental retardation, reproductive failure and increased susceptibility for infections.

Circulatory lipids usually exist in bound-form with proteins (lipoproteins), e.g. chylomicrons, high-density lipoproteins (HDL), low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL). HDL has lower fat and higher protein content than LDL/VLDL, hence considered as a *good cholesterol/fat.*

Requirement: Total and saturated fat intake should not exceed 20% and 10% of total caloric intake per day, respectively. In addition, minimum 2–3% of caloric requirements should be derived from EFAs and 0.3% from linolenic acid.

Sources: Dietary fats are derived from either a *visible source*, e.g. animal fats (ghee, vegetable oils) or *invisible sources* (cereals and pulses). In Indian diet, more than half of the fat is consumed as invisible fat.

Animal fats mainly contain saturated fatty acids and are poor source of EFA. Breast milk has enough EFAs to meet the baby's requirements. *All vegetable oils, except palm oil and coconut oil, are rich sources of EFA.*

Coconut oil is a rich source of medium chain triglycerides (MCT)—the only fat that does not require bile for absorption and directly absorbed into the portal vein. Hence, it is often used in malabsorption states, chronic hepatic disease and low birth weight newborns as a human milk fortifier.

Carbohydrates are most important source of ready as well as stored energy, as well as also essential for oxidation of fats and synthesis of certain non-EFAs.

Biochemistry: Carbohydrates are consumed either as free-sugars, e.g. *monosaccharides* (glucose, fructose and galactose) and *disaccharides* (sucrose, maltose, lactose) *or* as complex-sugars, e.g. *polysaccharides,* e.g. starch, cellulose, dextrin, etc. However, all carbohydrates are finally converted to glucose for use as metabolic fuel.

Normal glucose homeostasis is maintained by three important metabolic pathways: (a) *Glycogenesis*, e.g. conversion of free glucose and fat into glycogen for storage in liver and muscles, (b) *Glycogenolysis*, i.e. endogenous breakdown of hepatic/muscle glycogen to provide free glucose in starvation conditions, and (c) *Neoglucogenesis*, i.e. conversion of endogenous or dietary proteins and glycerol into glucose, in starvation states. Unlike hepatic glycogenolysis, glycogenolysis in muscles is an anaerobic process with production of lactic acidosis, responsible for starvation ketoacidosis.

Requirements: Carbohydrates should provide minimum 50–60% of caloric intake, preferably as complex-sugars to minimize post-prandial blood glucose fluctuations.

Sources: Starch is the commonest carbohydrate in diet, present in grains, legumes and tubers. Glycogen is present only in animal sources.

Fibers are complex carbohydrates like cellulose, hemicellulose, gums, pectins, and mucilages, etc., present in plant cell walls. Although of little caloric value due to their non-digestibility (2 calories/gram *vs* 4 calories/gram for other carbohydrates), presence of adequate fibers in diet is essential for colonic water absorption and softening of stools. While vegetarian diet contains adequate fibers, low-fiber non-vegetarian diet has been linked with higher risk of constipation, colonic cancers and hypercholesterolemia.

Vitamins are non-energy-yielding organic compounds, which act as *co-factors in many enzyme systems* to catalyze cellular metabolism. Although required in miniscule amounts, vitamins are essential for normal growth and maintenance of various body functions.

Vitamins may be divided into two groups, i.e. *fat-soluble* vitamins, e.g. vitamins A, D, E, K and *water-soluble* vitamins, e.g. those of B-complex group and vitamin C. Of these, vitamins D and K is also synthesized in body (endogenous source).

Vitamin-related abnormalities may be broadly divided into: (a) *deficiency* disorders, (b) *hypervitaminosis* or *excess* states, and (c) *dependency* states, i.e. inherited errors in metabolic/enzyme activity, dependent on related vitamins. *See* Chapter 6.2–6.7 for normal vitamin biochemistry, functions, sources and deficiency states.

Minerals are non-energy yielding inorganic compounds, which contribute to ~3–4% of body weight and mainly present in bones (~80%), muscles (~10%) and body fluids (~4%). Biologically important minerals are classified as:

- *Macrominerals,* which are present in substantial amounts and their nutritional requirement usually exceeds >100 mg/day. While some of these minerals are concentrated in tissues, e.g. bones and muscles, (e.g. calcium, magnesium, phosphorus, etc.), most of them are major electrolytes in body fluids as cations (Na^+, K^+, Ca^{++}, Mg^{++}) *or* anions (P^-, S^-, Cl^-).
- *Microminerals (trace elements),* constitute <250 µg/gm of tissue matrix, e.g. iron, iodine, zinc, fluorine, etc. Minerals present in still smaller amounts (<100 ng/g of matrix) are termed as *ultra-trace elements*. Despite miniscule requirements, trace elements play significant role in human health and disease (Ch 6.8).

Anti-oxidants are important phytochemicals present mainly in vegetables and fruits. These nutrients, also termed *free oxygen scavengers*, restrict the cellular damage caused by oxygen-free radicals and provide protection

against diseases related to free-radical damage, e.g. atherosclerosis, cancer, inflammatory joint diseases, asthma, diabetes, etc. Raw and fresh vegetables like green leafy vegetables, carrots, fresh fruits including citrus fruits and tomatoes have been identified as good sources of antioxidants (Ch 6.9).

5.2 BREASTFEEDING

Breast milk (BM) is the only food that a baby needs unto first 4–6 months of life and gives the best possible nutritional start to the neonate. *Exclusive breastfeeding (BF)* means that the neonate gets only breast milk and nothing else like honey, water, juices, tonic and medicines (unless prescribed) or any other animal milk.

5.2.1 COMPOSITION OF BREAST MILK

Volume output and composition of BM changes throughout lactation period to meet changing needs of growing infants.

Daily milk output in Indian mothers is ~30–60 ml during first 3 days of life (*colostrum*) that gradually peaks at ~2 months (600–700 ml) followed by gradual decline from 6–7 months onwards to <500 ml by one year and <300 ml by two years.

Colostrum is the thick yellow and sticky milk, produced during first 72 hours of life. Although secreted in small quantities, it is enough to meet the newborn's requirement during this period. Colostrum is not only rich in proteins and anti-infective factors, but also facilitates maturation of gastro-intestinal tract.

Transition milk is secreted between 3rd and 14th day. It has lesser protein and immunoglobulin content than colostrum, but relatively higher fat and sugar content to meet increasing energy requirements.

Mature milk, secreted from 15th day onwards, has further less proteins than the transitional milk, but more volume, fat and caloric content. Composition of mature milk also varies according to maternal diet as well as even during the course of a single breastfeed, as follows:

Fore milk flows at the start of each feed and is *relatively watery to satisfy the baby's thirst*, with lesser fat content, but rich in sugars, vitamins and minerals.

Hind milk, secreted in later part of feeding, is thicker than the fore milk with *higher fat content to satisfy the baby's hunger* and caloric needs.

Preterm milk from mothers of a preterm baby during first few days is qualitatively different from milk of term-mothers, with higher energy density, proteins and sodium content to meet their higher requirements. Preterm milk also contains less lactose and solutes, to adjust for maturational lactase deficiency and relative renal insufficiency in them. It achieves composition of term milk by 4–6 weeks.

5.2.2 ADVANTAGES OF BREASTFEEDING

Breast milk is *species-specific*, i.e. quantitatively and qualitatively most appropriate for human baby. Apart from nutritional superiority, breastfeeding also offers many other advantages to baby, mother, family and even to the community, as follows:

A. Nutritional superiority: BM is easily digestible and contains all essential nutrients in the right quantity and quality, as per baby's requirements **(Table 5.3)**. Major nutritional advantages of BM are as follows:

- *Energy* from BM is mainly derived from easily digestible carbohydrates, e.g. lactose.
- *Protein content* in BM, though less than in cow milk, is qualitatively superior due to:
  - *Better whey-casein ratio*: 75% of human milk proteins are easily digestible *whey proteins* or lactalbumin, unlike casein-rich cow milk, which is difficult to digest due to curd formation.

TABLE 5.3: Composition of human and cow milk

	Contents (100 ml)	*Human milk*	*Cow milk*
a.	**Energy** (cal)	67	70
b.	**Proteins**		
	Content (gm)	1.1	3.3
	Whey: Casein	75:25	22:78
	Essential amino acids	adequate	inadequate
c.	**Fats**		
	Content (gm)	3.8	3.8
	Type	PUFA	saturated
	Essential fatty acids	high	less
	Lipase enzyme	present	absent
d.	**Carbohydrates**		
	Content (gm)	7.8	4.8
	Lactose content	6.5%	4.5%
e.	**Water content**	88%	88%
f.	**Solute load** (gm)	0.2	0.7
	Sodium (mg)	0.2	0.7
	Potassium (mg)	0.5	1.5
g.	**Minerals** (mg)		
	Calcium	34	137
	Phosphorus	15	92
	Ca: P ratio	> 2:1	1.5:1
	Iron (mg/L)	0.5	~ 0.5
h.	**Vitamins**		
	Vitamin A (IU)	~10	>50
	Vitamin C (mg)	~ 6	~ 2
	Vitamin D (IU)	~ 5	~ 2.5
	Vitamin K (µg)	1.5	6.0

PUFA: Polyunsaturated fatty acids

  - *Essential amino acids (EAA):* BM contains all EAAs in appropriate concentrations to facilitate proper cognitive development, (e.g. taurine and cysteine), which are lacking in cow milk.
  - *High protein content* in animal milk increases risk of allergic disorders, due to absorption of macromolecules through immature gut mucosa.
- *Fat content* in BM is quantitatively comparable to cow milk, but with better quality, i.e. higher PUFA and EFA content. Cow milk is richer in saturated fats, which are difficult to digest and increases the risk of hypertension or heart disease in adult life. Human milk also contains *lipase enzyme*, essential for fat absorption.
- *Vitamin contents* in BM is adequate (except vitamin K), while cow milk is deficient in vitamins C and D. While low vitamin K content in BM is responsible for higher risk of hemorrhagic disease of newborn in breast-fed babies, it may be easily prevented by single dose prophylactic vitamin K supplement at birth.
- *Mineral (ash) content* of BM is much lower (1.5%) than in cow milk (>7.0%). High ash content in cow milk poses additional solute burden over developing kidney with limited concentration capability.
  - *Iron* content in BM is comparable to cow milk, but BM iron is better absorbed (~50%) than cow milk iron (10%), due to lesser phosphate load.
  - *Calcium* content is lesser in BM, though BM calcium is better absorbed and utilized due to appropriate Ca: P ratio. Consequently, tetany is less common in breastfed children.
- *Water:* BM contains adequate water (88%) and hence, no additional water is required in exclusively breastfed babies, with less risk of infections.

B. Anti-infective properties: BM is essentially sterile, except in presence of systemic or local (breast) maternal infection. Further, presence of various anti-infective substances in BM is responsible for lower incidence of gut and respiratory infections in breastfed infants. These factors include:

- *Humoral factors,* e.g.
  - Non-specific and specific IgG antibodies
  - Secretory IgA, for local immunity
- *Cellular factors,* e.g.
  - Phagocytic cells, e.g. macrophages
  - Cellular-release factors, e.g. lysozymes
- High complement activity
- *Organism-specific protective factors*, e.g.
  - Para amino benzoic acid (PABA) against malaria
  - Anti-staphylococcal factor
- Others, e.g.
  - *Bifidus factor*, to facilitates the growth of Lactobacillus bifidus in gut and prevents pathogenic colonization,
  - *Lactoferrin*, to binds the iron in gut and inhibit growth of pathogenic bacteria, e.g. *E. coli,* which need iron for their metabolism.
  - Lower pH of BM prevents bacterial overgrowth.

C. Emotional bonding: Breastfeeding creates an emotional bond between baby and mother, necessary for future growth, development, and parent-child adjustment.

D. Advantages to mother include:

- *Enhanced oxytocin secretion* to facilitate placental expulsion and uterine involution with less risk of post-partum hemorrhage.
- *Convenience and less workload*, obviating the need for boiling/mixing the top-milk. She also does not have to worry about the milk supply and spoilage.
- *Natural contraception:* Lactational amenorrhoea due to high prolactin levels is common during first 6 months, with ~98% protection.
- Lower incidence of breast and ovarian cancers.
- *Cosmetic recovery* with faster regaining of figure, due to more caloric consumption.

E. Advantages to family: Breastfeeding is a good economic practice for family as well, due to:

- Negligible cost, except the hidden expenses for additional nutrition to mother.
- Less health care expenses, due to lesser morbidity.
- Natural family spacing.

F. Advantages to the community include:

- *Ecological benefits* due to less consumption of natural resources for animal-milk production (fodder), boiling (fuel) and washing the utensils (water).
- Lesser morbidity in infants with less public health expenses.
- Population control, due lactational amenorrhoea.

5.2.3 PHYSIOLOGY OF LACTATION

Anatomically, the breast is made up of glandular tissue, supporting tissue and fat **(Fig. 5.1)**. There are ~20–25 alveoli in each breast, each lined by epithelial cells and surrounded by myoepithelial cells. Milk is secreted in alveoli by epithelial cells and pushed forward by contraction of myoepithelial cells. Each alveoli drains its output via lactiferous tubules and ducts into ~10–15 lactiferous sinuses, which lie below the areola and open out onto the nipple. The size of the breast depends on the amount of fat and supporting tissue and does not reflect on the milk-producing capacity.

Physiologically, lactation depends on two interdependent processes in mother: (a) production of milk (*prolactin reflex*), (b) secretion or ejection of milk (*oxytocin reflex*), as well as (c) actual sucking by the baby, dependent on neonatal reflexes.

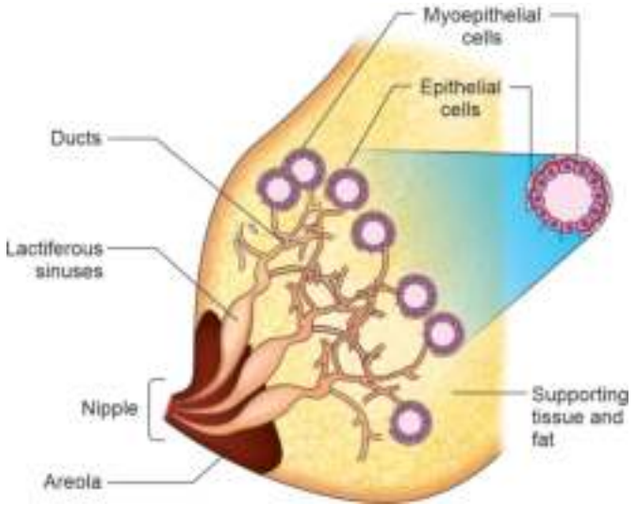


Fig. 5.1: **Normal breast anatomy.**

- **Production of milk (Prolactin reflex):** When a baby sucks, afferent impulses from nipple stimulate *prolactin* secretion from *anterior pituitary*. Prolactin acts on the milk-producing alveolar epithelial cells to stimulate milk secretion. Thus, the prolactin reflex depends on *how early, how often* and *how strongly* the baby sucks.
  - Prolactin activity and milk production is *facilitated* by: (a) adequate emptying of breasts after each feed, (b) early onset of lactation, (c) frequent suckling, (d) expression of breast milk, and (d) night feeds.
  - Prolactin secretion is *inhibited* by: (a) pre-lacteal feeds, (b) incorrect positioning, and (c) painful breast conditions, (d) physical or mental stress to mother.
- **Milk ejection/let down (Oxytocin reflex)** is also initiated during suckling when afferent impulses from nipple reach the *posterior pituitary* to stimulate *oxytocin* production. Oxytocin contracts the myo-epithelial cells surrounding the alveoli and lactiferous sinuses, to push the milk forward towards the nipple. The squeezing sensation in the breast during breastfeeding is a sign of a good "*let-down reflex*". Oxytocin secretion is affected by the physical and mental state of the mother.
  - Oxytocin activity and milk ejection is *enhanced* by: (a) sight and sound of baby, (b) pleasant thoughts of baby, and (c) maternal confidence in her ability to breastfeed.
  - Oxytocin secretion and milk ejection is *reduced* by: (a) mother's anxiety or low-confidence, (b) mental stress or worry, and (c) pain or discomfort during breastfeeding.
- **Actual sucking by baby (Neonatal reflexes):** Three neonatal reflexes, i.e. *sucking, swallowing* and *rooting* reflex, participate in milk extraction during breastfeeding.
  - *Rooting reflex* helps the baby to latch onto the nipple. When the breast or nipple touches the baby's chin, philtrum, upper lip or cheek, the baby opens his/her mouth to search for the nipple.
  - *Suckling reflex* helps the baby to draw milk by converting the nipple and areola into a *teat* pressed between the lower jaw and hard palate. Wave-like movements of tongue facilitate sucking. For successful lactation the baby must be well attached to the breast, with the nipple and most of the areola in his mouth.
  - *Swallowing reflex:* After every 2–3 sucks, collected milk is swallowed by baby, followed by deep breath. Each suck-swallow-breathe cycle lasts for ~2–3 second.

5.2.4 CORRECT BREASTFEEDING TECHNIQUES AND PRACTICES

Although breastfeeding (BF) is a norm in India, many problems during lactation may be avoided by following correct breastfeeding practices, discussed below:

- ***Antenatal preparation*** for successful lactation should begin with each ANC visit including: (a) breast examination to check protractility of nipples, (b) maternal counseling regarding importance and correct practices of breastfeeding, and (c) identification of 'at-risk' mothers, e.g. primipara, multipara, who did not breastfed to earlier babies or those with local nipple problems.
- ***Initiation of breastfeeding:*** *Breastfeeding should begin within the 30 minutes of vaginal delivery and as soon as possible after cesarean delivery*.

  Early feeding (a) stimulates prolactin secretion, (b) stimulates oxytocin secretion and help in placental expulsion with less risk of postpartum hemorrhage, (c) establishes emotional bonding, (d) prevents neonatal hypoglycemia, (e) provides immunoglobulin-rich colostrum, and (f) provides warmth to the baby by skin to skin contact.

  Breast crawl is a very useful practice to achieve early initiation of BF. It involves placing the newborn on mother's abdomen soon after the delivery that allows him/her to find mother's breast on its own and decide when to take the first breastfeed **(Fig. 5.2)**.
- ***No pre-lacteal feeds:*** Any top-feeds, given to the baby before breastfeeding are termed as *pre-lacteal feed*. This includes water, sugar water, honey, gripe water, etc. Pre-lacteal feeds are strongly discouraged due to the risk of: (a) enteral infections, (b) nipple confusion*, and (c) poor sucking efforts by partly satisfied baby with consequent decrease in the BM output.

  When pre-lacteal feeds are given by a syringe, bottle or spoon, easy flow of milk may cause *nipple confusion,* i.e. confuse the baby to properly latch and suck during subsequent breastfeeding.

Fig. 5.2: **Breast crawl.**

Fig. 5.3: **Good attachment (latching) on breast.**

- **Rooming in,** i.e. *keeping the baby with the mother in the same room and on the bed* helps to maintain the baby's temperature, initiate and maintain breastfeeding and develop emotional bonding.
- *Schedule/ frequency of feeding:* Baby should be fed as and when required, i.e. *demand feeding*, rather than to fix-up a *scheduled feeding*. In fact, a normal baby itself develops a flexible schedule by the end of 2 weeks, when she/he demands the feeds ~2–3 hourly.

  If a baby demands more frequently, it is possible that either: (a) the duration of feeding is too short *or* (b) she/he is getting only foremilk.
- *Hygiene:* There is no need to wash breasts before feeding, though general hygiene by daily bath should be maintained.
- *Environment:* Baby should be breastfed in a peaceful and tension-free environment, without hurry and worry of domestic chorus, to avoid forcible interruptions during breastfeeding and consequent problems.
- *Breastfeeding position:* Any BF position is acceptable, provided mother is comfortable and baby is well-attached to the breast. Some commonly used positions are:
  - *Indian position*, i.e. mother sitting cross-legged, with a back support.
  - *Cradle position*, i.e. mother cradling the baby in her arms with the forearm supporting his/her head.
  - *Football-hold position* is useful to feed the twins. In this, the baby is held under the arm of mother with feet pointing backward, abdomen touching mother's chest and body supported by mother's arm.
  - *Side-lying position* is useful for night feeds, BF in immediate post-cesarean period and in sick mother. Mother and baby lie down facing each other with mother's hand supporting baby's back.
  - *Supine position* is helpful in post-cesarean period or when milk-flow from the breast is in excess to the baby's speed of sucking. In this, mother feeds in supine position with baby held onto her abdomen.

  Signs of a good breastfeeding position are:
  1. Baby's whole body is supported, not just the neck or shoulders,
  2. Baby's head, neck and body are in straight line, without any twist or bending. Head can be slightly extended to bring chin closer to the breast,
  3. Baby is held close, with body turned toward mother and abdomens touching each other,
  4. Baby should be facing the breast, with nose at the level of mother's nipple.
- *Proper attachment* of the baby at the breast is essential to prevent painful nipple problems in mother as well as to ensure adequate intake by baby.

  Signs of good attachment include **(Fig. 5.3)**:
  1. Baby's mouth is wide open,
  2. His/her lower lip is everted,
  3. His/her chin is touching the mother's breast,
  4. Most of the mother's nipple and areola is inside his/her mouth, except a small of upper areola. No part of lower areola should be visible.
- *Effective sucking:* Normally baby suckles 2–3 times by pressing the areola with the tongue against the hard palate to squeeze-out the milk, before pausing to swallow the collected milk.

  Signs of effective sucking include:
  1. Baby's cheeks are full and not hollow,
  2. Baby is calm and relaxed,
  3. Mother does not feel any pain.
- *Duration of each feed* should be decided by the baby (some are fast-feeders while others are slow-feeders) and she/he should be allowed to release the breast on its own. As a baby needs both-the *watery foremilk* to satisfy the thirst as well as the *fatty hind-milk* to satisfy the hunger, one breast should be emptied first before the other is offered. In case, baby is unable to empty

Fig. 5.4: **Burping.**

both breasts at one time, other breast should be offered first during subsequent feeding.

- *Burping:* Babies swallow lot of air during BF, especially if not properly attached to the breast. This *aerophagia*, may lead to abdominal discomfort, colic, regurgitation of feeds and rarely, aspiration. *Burping* by placing the baby over shoulders in upright position for 5–10 minutes with gentle stroking of back after feeds, helps to evacuate swallowed air **(Fig. 5.4)**.
- *Expression of breast milk* is advised in cases of: (a) painful breast engorgement, (b) any contraindication for breastfeeding (to discard), or (c) separation of mother and baby due to sickness or other causes. (see Ch 5.4.1)

5.2.5 COMMON BREASTFEEDING PROBLEMS

Common BF problems may be broadly divided into three categories: (I) breast and nipple problems, (II) partial or complete lactation failure, and (III) breastfeeding in special situations, e.g. sick mother, sick baby or working mother.

I. Breast and nipple problems are very common and often used as an excuse to start top-feeding, despite adequate milk output. These problems are more common in primipara mothers and include:

- **Flat or inverted nipples** may prevent proper attachment of baby to the breast. Flat nipples become prominent when pinched at base, while inverted nipples go in. These problems can be easily identified by antenatal breast examination. Flat nipples usually do not pose any feeding problems and can be managed easily by assuring mother and some modification in feeding positions. Persistently flat or inverted nipples may be managed by: (a) nipple-stretching exercises

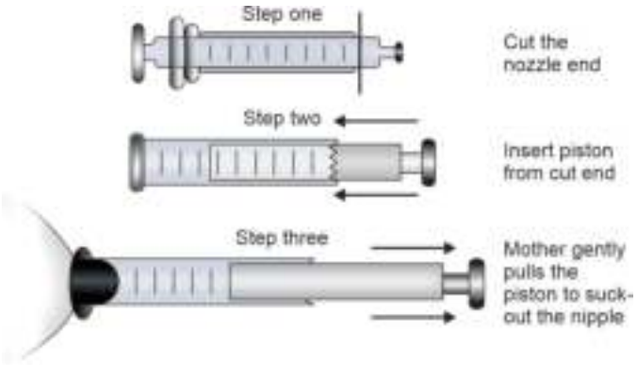


Fig. 5.5: **Syringe method for flat/inverted nipples.**

(pulling the nipple and rolling it between fingers), (b) use of a breast pump to pull the nipple out before every feed, or (c) syringe method.

Syringe method *(Kesri method)* is a simple suction device, prepared by cutting the nozzle end of a syringe and inverting its piston **(Fig. 5.5)**. When the smooth end of syringe is pressed against the nipple and piston is pulled gently, the inverted nipple pulls out of the breast tissue. This should be done before each breastfeed.

- **Sore nipples** are painful, tender nipples with or without cracks or bleed, caused by: (a) wrong positioning/attachment of baby on the breast, (b) forcible separation of baby while sucking, (c) repeated washing of breasts with soap solutions before feeds, (d) local fungal infections (thrush).

  Sore nipples are managed by: (a) correct positioning/attachment of baby, (b) starting each feed on the less affected breast, (c) application of hind-milk on the nipple as *emollient*, and (d) local anti-fungal treatment, if necessary.
- **Breast engorgement** indicates inadequate expression of milk despite adequate production, leading to hard, painful, warm and swollen breasts. It is usually caused by infrequent breastfeeding due to: (a) delayed initiation at birth, (b) maternal/neonatal sickness or (c) painful breast and nipple conditions **(Fig. 5.6)**.

  Most of these cases are self-limiting and can be prevented or managed by: (a) frequent demand feeding, (b) frequent expression of milk, if baby/mother is sick, and (c) local hot-water compresses to relieve pain.
- **Breast abscess (mastitis)** may develop due to infection of engorged breast, with cracked nipple as a portal of entry for infection **(Fig. 5.6)**.

  These cases are treated with: (a) antibiotics and surgical drainage, (b) symptomatic therapy with analgesics and hot compresses (breast massage should be avoided), and (c) frequent expression of milk, which may then be fed to the baby.

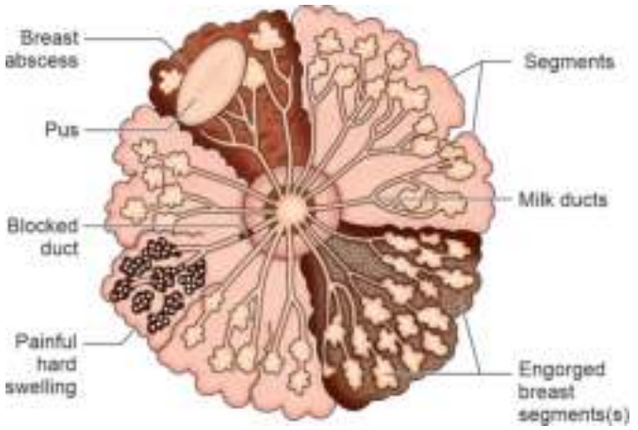


Fig. 5.6: Common painful breast conditions.

TABLE 5.4: Causes of lactation failure

I. Psychological causes ***(↓ oxytocin activity)***
- Lack of self-confidence
  - Primigravidas and teen mothers (inexperience)
  - Unsuccessful breastfeeding in earlier pregnancy
  - Inadequate antenatal counseling
- Physical or mental stress
  - Mental anxiety or worry
  - Physical stress, e.g. working mothers
  - Wrong advice/counseling from family

II. Incorrect breastfeeding practices ***(↓ prolactin activity)***
- Prelacteal feeds and delayed onset of breastfeeding
- Infrequent or less vigorous breastfeeding
  - Painful breast or nipple conditions
  - Weak or preterm baby
  - Schedule feeding
  - Wrong positions or attachment

III. Physical causes ***(true lactation failure)***
- Extreme maternal undernutrition
- Extremely sick mother

II. Lactational failure is defined as *low milk output* in the mother, *inadequate to meet baby's requirements*. It may be *primary* since delivery or *secondary* after successful initiation of breastfeeding at birth; partial *or* complete; transient *or* permanent; and true *or* perceived.

Causes: *True lactation failure is extremely rare.* In most cases, it is a consequence of complex cycle, involving temporary delay in the initiation of BM output due to any cause > maternal anxiety > wrong advice from others > initiation of supplementary feeds > reduced frequency and duration of BF > further decrease in milk-output **(Table 5.4)**.

Management of lactation failure mainly aims to boost mother's confidence in her ability to breastfeeding, eliminate causative factors and advise correct breast-feeding practices. Continuous monitoring is necessary to prevent recurrence of problem. Important steps in lactation management include:

Step I. Assess the BM output, which is probably adequate if: (1) baby is gaining adequate weight, i.e. ~20–30 gm/day after 10th day; (2) baby is passing the adequate urine, i.e. ~6–8 times a day; (3) baby is sleeping comfortably for 1–2 hours after breastfeeding; (4) mother feels a sense of fullness in the breast before next feed time; (5) milk starts dripping from other breast, when the baby is sucking on one breast. *Test weighing*, i.e. weighing the baby before and after feeds, is rarely required.

Step II. Reassure and counsel the mother, if milk output is adequate. Let her understand the indicators of adequate BM output (as above).

Step III. Identify and eliminate causative factors, e.g. local breast/nipple problems, improper attachment, wrong feeding practices, misguidance from others, partial bottle-feeding or maternal illness. Identification of the cause requires detailed history of family environment and breastfeeding practices, observation at the time of BF and physical evaluation of mother/baby.

Step IV. Boost the milk output: Many *galactagogues,* e.g. special foods, herbs, (e.g. satavari), drinks or medications, (e.g. PO metaclopramide 10–15 mg TDS) are claimed to increase milk production by stimulating prolactin secretion. However, most of them have only placebo effect.

The best galactagogue is a nutritious diet to mother and a healthy, exclusively demand-fed baby, vigorously sucking in correct position.

Step V. Re-lactation is possible in some cases of secondary LF, even after many days with following measures:

- ***Non-nutritive sucking:*** Simplest measure to establish re-lactation is to place the baby on the breast at least 8–10 times/day for 10–15 minutes every time, even in the absence of milk output, termed as *non-nutritive sucking.*
- ***Drip and drop method*** may be useful to re-establish lactation in mothers even after many weeks. Lower end of a nasogastric tube connected to milk-filled syringe is fixed with an adhesive tape over mother's nipple and baby is encouraged to suck on nipple while milk is gradually dripped over it. Since baby gets the milk through the tube, she/he is encouraged to suck further, which may help re-lactation.

Step VI. Alternative modes of feeding, e.g. wet-nursing by other lactating mother in family, milk sourced from human milk banking or top-feeding are very rarely indicated, when all efforts to re-establish lactation fail.

III. Breastfeeding in special situations: *There are no absolute contraindications for breastfeeding except* when mother is on certain drugs **(Table 5.5)**, which are unavoidable, excreted in breast milk and can cause serious problems in baby. However, following situations are common in clinical practice, which requires a considered review of BF advisability, sustainability and modifications.

TABLE 5.5: Medications in lactating mothers

Absolutely contraindicated:
(discontinue breastfeeding, if unavoidable)
- Cytotoxic agents
- Radioactive agents
- Lithium

To be avoided:
(use alternatives, if necessary)
- NSAIDs (use paracetamol)
- *Antibiotics:* Sulpha, chloramphenicol, tetracycline
- Estrogen/progesterone preparations
- Thiazide diuretics
- Sulfonylureas
- Oral anticoagulants

To be used with caution:
(continue breastfeeding but monitor toxicity)
- Anti-convulsants, e.g. phenobarb, phenytoin
- Sedatives, e.g. diazepam, phenothiazines
- *Anti-asthma:* Theophylline
- *Others:* Laxatives, quinine, ethambutol

Cesarean delivery: While some mothers may be apprehensive to breastfeed soon after LSCS due to fear of pain and inappropriate advice, they should be motivated to initiate BF as soon as possible, preferably within 1 hour of birth. Mother must be helped to find a comfortable position to breastfeed, e.g. supine position on first day, side-lying position on second day and sitting position subsequently.

Working mothers: Employers must be encouraged to: (a) permit longer maternity/lactation leave for at least 6 months after delivery, (b) permit flexible work-timings for lactating mothers, (c) provide a crèche at workplace. Even in absence of these facilities, employed mothers can successfully continue BF after joining the duty by: (a) breastfeeding the baby while at home, just before leaving for work and immediately on returning home, as well as (b) expressing the milk an hour before leaving the home (which can be stored up to 8 hours at room temperature) and fed to the baby later by caretaker with the help of *Bondla or katori*/spoon.

Maternal infections: Some maternal infections, e.g. HIV, CMV, HBV, etc. may be transmitted to the baby via breast milk, though the risk of transmission is usually less than the disadvantages of top-feeding. HBV positive mothers should continue exclusive BF till 6 months of age, like others. Similarly, BF is default feeding in HIV positive mothers as well in view of universal ART to mother and universal prophylaxis to the exposed baby (Ch 10.28). Top feeding should be considered only if ***AFASS criteria*** (**A**cceptable, **F**easible, **A**ffordable, **S**ustainable and **S**afe) is fulfilled.

Serious physical illness in mother: Most sick mothers can successfully breastfeeding their baby, either directly or through using expressed breast milk. Manual expression should continue even if breastfeeding is not possible, to prevent breast engorgement. Temporary discontinuation of breastfeeding is required if mother is: (a) seriously sick, e.g. shock, coma, etc. or (b) on contraindicated medications.

Serious psychiatric illness in mother, requires discontinuation of breastfeeding if: (a) mother is on lithium therapy, or (b) baby needs to be separated due to violent/unstable behavior in mothers.

Maternal medications: Considerable quantities of certain drugs are excreted in BM, which may produce untoward effects on baby **(Table 5.5)**. In these cases, three options are available: (a) temporary or permanent discontinuation of breastfeeding, (b) switch-over to alternate medications, if possible, and (c) continuation of breastfeeding with closer vigil for adverse events. Only the use of cytotoxic or radioactive drugs or lithium in mother are absolute contraindications for BF.

Preterm babies: Mode of feeding in preterms usually depends on their maturity. Most of the non-sick babies >1500 gm can be safely fed on breast directly or on EBM by katori/spoon/Bondla. Babies between 1200–1500 gm may need nasogastric EBM during early days. Mother's own milk as EBM is the first choice in babies who cannot breastfeed directly, followed by pasteurized donor milk or preterm formula.

Babies with cleft-palate may not generate enough suction to express breast milk. If required, they may be fed directly on breast by using the obturators or may be given expressed breast milk by katori/spoon, etc. Semi-upright position is recommended in these cases to reduce nasal regurgitation and reflux of breast milk into the eustachian tubes.

Serious physical illness in baby: Unless oral feeding is contraindicated, breastfeeding should continue either directly or through expressed breast milk. In cases when oral feeding is not possible, e.g. due to extreme prematurity, critical sickness or surgery in newborn, manual expression of mother's breast should continue to maintain milk output for future use.

Neonatal death: In this unfortunate situation, the lactation reduces spontaneously due to lack of stimulation, though the *drying-up* process may be hastened with some anti-galctogogues, e.g. *bromocriptine*, to prevent breast engorgement and maternal discomfort.

Breastfeeding during travel and social events should continue with minor adjustments in timings and practice.

5.2.6 LACTATION COUNSELING

Breastfeeding plays a crucial role in health growth and development during early infancy. While it is a natural

process, some mothers may need support to successfully establish, maintain and continue BF till desired period.

Objectives: Lactation counseling is a process to encourage and support these mothers for successful lactation and includes:

- Informing mothers about advantages of breastfeeding to baby as well as to mother.
- Demonstrating mothers about correct BF practices.
- Assessing the position and attachment during BF.
- Identify and mange breast and nipple problems, which may hinder BF.
- Provide solutions to mothers for BF in special circumstances and encourage them to continue breastfeeding.

Antenatal lactation counseling: Effort to ensure successful BF must ideally begin from the first antenatal visit to:

- Prime the expectant mother about advantages of BF,
- Prepare her to initiate BF immediately after the delivery,
- Assess the general health to convince her in the ability to breastfeed,
- Examine breasts for local problems, e.g. inverted nipples, and advice for corrective manoeuvres, e.g. manipulative pulling or syringe method,
- Identify potential barriers or contraindications for BF, e.g. HIV positive status or drug therapy.

Antenatal lactation counseling should specially focus on: (a) primpara mothers or (b) mothers who did not BF successfully during previous pregnancy.

Postnatal lactation counseling must begin in the delivery room to initiate BF as early as possible and should continue during each visit in postnatal ward as well as on follow-up after discharge. BF problems are more common in LSCS and low birth weight babies. Postnatal counseling must include:

- History related to timing of first feed, use of prelacteal feeds, frequency and duration of feeding, burping after feeds and any problems during BF. History should also include the state of baby after BF, e.g. cry, sleep and urine frequency to assess the adequate of feeding.
- Observation of mother while breastfeeding, to ensure correct breastfeeding position, proper attachment and signs of effective sucking, discussed earlier.
- Examine the breasts for any local breast and nipple problem, if required.
- Examine the baby for any problem as well as the weight gain after first week of life.
- Offered solutions to her problems or apprehension to encourage continuance of BF.

Mother's privacy should always be respected while observing the BF or examining the breasts, which should always be done with her explicit consent and in presence of other female members/nurse, when done by a male health care worker.

Many online and off-line courses are available at present to train health care workers for better lactation counseling practices.

5.3 BABY FRIENDLY HOSPITAL INITIATIVE

Baby friendly hospital initiative (BFHI) is a worldwide movement, launched in 1992 to *protect, promote and support exclusive breastfeeding*, jointly sponsored by WHO, UNICEF and allied organizations. Revised and expanded version of BFHI has been implemented by UNICEF and WHO in 2009.

Objectives: BFHI aims to:

- Promote correct breastfeeding practices at delivery centers,
- Certify the hospitals following these practices,
- Train and motivate the staff of these hospitals.

Promotion of other baby and mother friendly activities, e.g. antenatal care, essential newborn care, immunization and appropriate management of diarrhea or acute respiratory infections, has been included in further expansion of this program, termed ***BFHI plus.***

Breastfeeding policy: A baby-friendly hospital is expected to follow and promote correct breastfeeding practices, included in a well-defined and written breastfeeding policy.

BFHI certification: A hospital is certified as *baby friendly* after careful evaluation and physical verification of breastfeeding practices by trained and certified assessors.

The certifying criteria for a baby-friendly hospital are: (a) having minimum 250 deliveries/year, (b) following *ten steps for successful breastfeeding* **(Table 5.6)**, and (c) creating baby-friendly community in their locality.

TABLE 5.6: Ten steps to successful lactation

1.	A written breastfeeding policy
2.	Training of health-staff in breastfeeding promotional skills
3.	Antenatal counseling towards breastfeeding
4.	Initiation of breastfeeding, within 30 minutes of delivery
5.	Exclusive breastfeeding and no pre-lacteal feeds
6.	Practicing *rooming-in*
7.	Encourage demand feeding
8.	No artificial teats/pacifiers to breastfeeding infants
9.	Correct breastfeeding practices and continuance of lactation by EBM, even if the baby is separated from mother for medical reasons
10.	Breastfeeding support groups

EBM : Expressed breast milk

A hospital also benefits by BFHI certification as it gets: (a) public recognition and more maternity work input, (b) IEC material for distribution to mothers, and (c) better neonatal survival and lower morbidity.

5.4 ALTERNATIVE INFANT FEEDING

While breastfeeding is the best option for early infant feeding in first 6 months of life, sometimes it may be necessary to explore other options in cases when it is either not possible or contraindicated due to any reason. Three options in these cases include use of: (a) expressed breast milk, (b) milk from human milk banking, and (c) top feeding with animal or formula feeds. Wet nursing by another lactating women is an option, which is rarely feasible in current situation.

5.4.1 EXPRESSED BREAST MILK

Expression of breast milk is advised in cases of: (a) painful breast engorgement, (b) any contraindication for breastfeeding (to discard), or (c) separation of mother and baby due to sickness or other causes.

Milk may be expressed manually *or* with a breast pump, though manual expression is more hygienic, economical and convenient. The mother herself or a relative may express milk in a wide-mouth clean container by applying continuous forward pressure over lactiferous sinuses below the areola.

Manual expression of milk requires following steps:

- Wash the hands and massage the breast gently towards the nipples,
- Place the thumb and index finger opposite each other just outside the areola,
- Press back towards the chest to gently squeeze the milk out of nipple,
- Repeat same steps in different positions around the areola.

This expressed breast milk (EBM) may then either be fed to the baby by a *bondla* or nasogastric tube or discarded. BM can be stored at room temperature for 8 hours, in refrigerator for 24 hours, or in deep freezers, i.e. *breast-milk banks* at –20°C, up to 3 months. Stored EBM should be brought to room temperature before feeding by keeping outside, but it should never be heated or stirred to dissolve the fat globules.

5.4.2 HUMAN MILK BANKING

Human milk banking in India was started in 1989 in Mumbai and is now available at many major centers of the country. It offers a solution to mothers who cannot feed their babies temporarily, especially when they are in hospital or intensive care unit. It involves:

- Collection of milk by voluntary donations from lactating mothers,
- Screening of donor's milk for common infections including cultures to detect bacterial contamination,
- Pasteurization of donor's milk by *Holder method*, before storage in stringent environmental conditions,
- Supply of this stored milk for feeding of sick and small newborns, for whom the mother's milk is no available.

While donor's milk from milk bank is inferior to the mother's own milk due to loss of some immunological and nutritional ingredients during pasteurization and storage, it still retains many advantages of breast milk and is tolerated better than formula milk with lesser risk of (a) infections, e.g. necrotizing enterocolitis (b) feed intolerance as well as risk of (c) metabolic syndromes in later life, with better developmental scores.

5.4.3 TOP FEEDING

Top feeding, i.e. *feeding of milk other than the breast milk in early infancy*, should be strictly discouraged. However, it may be necessary in rare instances of: (a) true lactation failure, (b) maternal death/serious sickness, or (c) any absolute/relative contraindication for breastfeeding.

Top feeding may be loosely classified as: (a) exclusive top feeding, or (b) supplementary top feeding along with breastfeeding, e.g. in partial lactation failure. Important issues in top feeding are as follows:

- **Which milk to use?** Milk sourced from human milk bank is the best option if mother's own milk is not available, though might be difficult to sustain post-discharge. Although many age-appropriate commercial formula feeds are available, prohibitive cost and risk of incorrect dilution by illiterate and poor mothers render them unsuitable for regular use in India. Dried skimmed milk powders or evaporated/condensed milks are also unsuitable for top feeding due to same reasons as well as unbalanced composition. Skimmed milk powders have high protein and solute content (risk of dehydration), while condensed milk has excess carbohydrates (risk of diarrhea).

  Pasteurized or fresh-boiled cow milk remains the most practical, though not the best alternative to breastfeeding in resource-limited population, if top feeding is unavoidable. Composition of the cow's milk is nearest to the breast milk except high protein load, which may be reduced by dilution. It should be diluted with water in 1:1 ratio during first two weeks (longer in preterms) and in 2:1 ratio during next two weeks. Undiluted cow milk may be used after one month of age.

  Commercial formulas are specially prepared to bring their composition nearest to BM after dilution and hence, if used at all, should be diluted strictly according to the manufacturer's instructions.

Fig. 5.7: Bondla feeding.

TABLE 5.7: Complications of top-feeding.

Related to the milk/formula:
- Under nutrition *(over-diluted milk)*
- Dehydration *(concentrated formula feeds)*
- Oral mucosal scalding *(hot feeds)*
- Constipation *(high solute load)*
- Allergic problems *(high protein content)*
- Recurrent respiratory infections *(no immune factors)*

Related to the bottle
- Diarrhea (contaminated bottle)
- Overfeeding or underfeeding
- Aerophagia *due to wrong bottle position*
- Nipple confusion – difficulty in simultaneous breastfeeding
- Weaning problems (refusal to part with bottle)
- Defective dentition/caries (sp. with night feeds)

- **How much to give?** Quantity of top milk depends on baby's age, gestation and weight. As a general rule, top-milk should provide ~110–120 cal/kg/day. And calculated amount should be divided into 8 rations (3 hourly) during first two month and 6–7 ratios (4 hourly) subsequently, to be given during each feed. A term baby normally accepts ~50 ml feeds during first 2 weeks, ~100 ml between 2–8 weeks and ~150–250 ml subsequently.
- **How to give?** Top feeding must be given by *katori* and spoon, or indigenously designed utensils, e.g. *bondla or paladi* **(Fig. 5.7)**. Although convenient, risk of infection and other complications is maximum with bottle-feeding, which should be avoided as far as possible.
- **Which precautions to take?** Important precautions, necessary to prevent complications of top feeding **(Table 5.7)** are:
  - *Proper preparation of feeds*
    - Proper quantity and dilution of feed
    - Use of fresh boiled milk/diluted formula
    - Proper temperature of feed
  - *Proper preparation of feeding equipment*
    - Proper sterilization of feeding utensil/bottle
    - Proper teat-hole size to allow *drop by drop* flow of milk from inverted bottle.
  - *Correct technique of feeding*
    - Semi-upright position to avoid aspiration
    - Burping after feeding.
  - *Early vitamin/mineral supplements*, as vitamin C and iron are deficient in cow milk.
- **How to sterilize feeding bottle/utensils?** While bottle feeding is strongly discouraged, proper sterilization is necessary, if unavoidable. Bottle and nipple may be sterilized by *boiling** or *chemical sterilization* by dipping for 10 minutes in *milton solution* (2% sodium hypochlorite). Other feeding utensils, e.g. *bondla, katori*, spoon, etc. need not be boiled but should be properly cleaned with running or warm water.

  *Before boiling, bottle should be properly cleaned with brush and lukewarm salt-water to remove the stickiness. Subsequently, bottle and nipple should be boiled for 15–20 minutes and 5 minutes respectively and left in container itself, till required, to prevent re-contamination.

Infant Milk Substitutes, Feeding Bottles and Infants Food Act, 1992

Infant Milk Substitutes, Feeding Bottles and Infants Food Act, 1992 (Amended 2003) is a strong legal deterrent against top feeding and includes in brief:
- No person shall advertise or promote of infant milk substitutes to public in any form including inducements, donations or distribution of educational materials.
- No container of infant milk substitute should use words, e.g. humanized, recommended, complete food or images of healthy babies on the label. It should also carry warnings as prescribed in the act.
- No poster or IEC material should be distributed in the hospitals except to registered medical practitioners.
- No inducement of any kind, e.g. money, gifts or sponsorships should be offered to health workers
- No commission on the basis of sales volume should be provided to distributors, sellers and others in supply chain.

Any violation of the act may attract severe fine and punishment, including imprisonment up to 3 years.

5.5 COMPLEMENTARY FEEDING

Complementary feeding (weaning) is defined as *"gradual introduction of semi-solids and solids in baby's diet apart from breast milk, to meet their growing demands, usually at 6 months."*

Note that weaning is a complementary process and *not the discontinuation* of breastfeeding, which should continue as long as possible, preferably till 2 years of age.

Purpose: BM is all that a baby needs till first 4–6 months of life. At this age, introduction of complementary feeds is necessary as:

a. Breast milk output reaches a plateau (600–700 ml/day) by this age,
b. Growing baby's dietary requirements exceed the supply from mother's milk,
c. Baby's stomach is ready to receive and digest food, other than the breast milk.

- *Early* introduction of complementary feeding before 6 months is harmful due to reduction in BM intake and higher risk of infections and allergies as well as obesity in later life.
- *Late* introduction of complementary feeding beyond 6 months affects optimal growth of the baby and may creates difficulties in subsequent weaning due to development of *breast-affinity* in baby.

Characteristics of complementary foods: Common complementary foods used at different ages in infants and young children are shown in **Table 5.8**. Ideal complementary foods should be:

- **Age-appropriate** with consistency appropriate to the developmental readiness of the child in munching, chewing and swallowing. Complementary feeding must begin with soft, homogeneous, thinner and bland feeds, (e.g. Porridge), followed by thicker *mashed* foods and lastly, the *chewable* foods. Gut mucosa is relatively permeable to undigested proteins in early infancy, which may induce allergic mechanisms. Hence, *eggs should not be introduced in diet before 6 months.*
- **Energy-dense** to account for small stomach size of infants. Meals can be made energy-dense by thickening them and adding ghee/butter/oil or jaggery. Energy value may also be enhanced by using fermented, sprouted or toasted grains for preparation of meals.
- **Home-made and less expensive:** Complementary foods must be based on staple diet of the family. Commercial foods must be avoided as due to cost and potential risk of harmful additives or high salt content. Fortified foods with iron, iodized salt, vitamin A, etc. must be encouraged. Junk foods should be avoided.

TABLE 5.8: Common weaning foods* for Indian children

Age 6–8 months (2–3 meals/day; 2–3 tablespoonful/meal)
- Thickened fruit juices and soups
- Mashed fruits, e.g. banana, papaya, cheekoo, etc.
- Boiled-mashed vegetables, e.g. carrot, potatoes, etc.
- Milk-cereal porridge (ragi/nachni/suji), kheer, etc.

Age 9–11 months (3–4 meals/day; ~ ½ cup/meal)
- Cereal-pulse combinations, e.g. khichri, rice-dal
- Chewable foods, softened in dal, e.g. bread, chapati
- Eggs (Not <6 months due to risk of allergy in later life)
- *Non-veg:*, e.g. mashed chicken, fish, by 7–8 months

Age 12–23 months (3–4 meals/day; ~ 1 cup/meal)
- All foods eaten by the family, though less spicy

*Add ghee/oil to increase caloric content

- **Culturally and culinary acceptable:** Non-vegetarian foods are richer in proteins, though vegetarian foods are equally good, if used in combination of cereals and pulses, e.g. khichadi. While some babies may prefer salty or sweet feeds, addition of salt or sugar in complementary feeds is not recommended till 2 years of age.
- **Fresh and hygienic** at all levels of preparation, storage and feeding. Handwashing must be encouraged during preparation/feeding of meals and cooked food must be consumed within 1–2 hours, unless refrigerated.

Principles of complementary feeding: Weaning should be a gradual and pleasant experience to the baby and some important principles include:

- ***Introduction of feeds:*** Start with one food item at a time and continue it for a week or so, till the baby gets used to it before adding next item. Multiple food items should not be started at same time. Increase the quantity, consistency and frequency of each feed gradually, till desired intake is achieved.
- ***Mode of feeding:*** Feed with a *katori* and spoon and never use the bottle. Older children should be encouraged to feed from separate plate, to assess the exact intake. Self-feeding should be encouraged, with fingers/spoon.
- ***Dietary diversity:*** Children should receive complementary foods from at least 4 of the following seven food groups (also termed as *minimum dietary diversity*): (1) grains, roots and tubers, (2) legumes and nuts, (3) dairy products; (4) flesh foods, e.g. meat fish, poultry, (5) eggs, (6) vitamin-A rich fruits and vegetables, (7) other fruits and vegetables.
- ***Frequency of feeding*** *(Minimum meal frequency)**:*** Babies should be fed complementary feeds at least 2–3 times during 6–8 months and 3–4 times during 9–23 months of age. Those, who are not on breast feeds simultaneously must be fed at least 4 times during 6–23 months. Inter-meals snacks of good nutritive value must be encouraged in addition to regular meals. However, junk foods should be strictly avoided as snacks.
- ***Supplements:*** Iron rich/fortified foods or iron supplements should be provided to all infants from 6 months of age.
- ***Target:*** Weaning must be complete by 1 year of age, when baby should be qualitatively eating the regular family diet, albeit in quantities about half of the mother's diet. Breastfeeding should continue as long as possible, as a source of supplementary nutrition.
- ***Responsive feeding.*** Young children should be encouraged to take feed by praising them. Forced feeding with threats and punishment interfere with

development of good feeding habits. Minimize the distractions during feeding.

- ***Breastfeeding*** should be continued till 2 years of age, along with CF.
- ***Feeding during sickness:*** Both, BF and CF should be continued even when the child is sick, if it is tolerated.

Assessment of complementary feeding: All children aged 6 months to 2 years must be assessed for adequacy of CF during each visit with following questions:

- At what age, CF were introduced in diet ?
- Which CFs are being used at present, including the consistency of these feeds ?
- How frequently CF are given in last 24 hours to compare with recommended minimal meal frequency?
- Which CF were given in last 24 hours to compare with recommended minimum meal diversity?
- Whether breastfeeding has been continued and how frequently it is being given ?
- Whether iron supplements are also being given ?
- Whether feeding is/was continued during the sickness of the child.

Mother should be counseled about correct CF practices, as described above under principles of CF. Any deviation from these norms/practices may significantly affect the nutritional status of infant and needs careful monitoring.

5.6 INFANT AND YOUNG CHILD FEEDING GUIDELINES

WHO and UNICEF jointly developed a global strategy for *infant and young child feeding* (IYCF) in 2003, considering the impact of feeding practices and nutritional interventions during critical window period of first 1000 days of life (270 days *in-utero and* first two years after birth) on growth, development, health and survival in children. First national IYCF guidelines were formulated by Government of India in 2004 and revised subsequently.

IYCF guidelines are a *set of recommendations* for appropriate feeding of newborn and children *up to two years of age*. Important components of these guidelines, including those suggested by IAP in 2016 are as follows:

- **Early initiation of breastfeeding** as early as possible after birth, ideally within first hour, including in those born by cesarean section. Colostrum should not be discarded but to be fed to newborn and no pre-lacteal fluid should be given. Antenatal counseling, *rooming-in* and *breast-crawl* are useful strategies to assist early initiation of breastfeeding.
- **Exclusive breastfeeding for the first six months.** No other foods or fluids, even the water, are permitted (except medicines). Useful strategies to promote exclusive breastfeeding include: *demand feeding*, early management of breast/nipple problems and workplace support, e.g. lactation leave/lactation rooms. Brestfeeding should be continued during maternal illnesses unless contraindicated.
- **Timely introduction of complementary feeding** from 6 months of age with introduction of solids and semisolids to complement breast milk, which should continue *ad libitum* till 2 years of age. *Timely* means introducing the complementary feeds when the need for energy and nutrients exceeds that provided through exclusive breastfeeding. The term "complementary feeding" and not "weaning" should be used.
- **Age-appropriate complementary feeding** for children 6–23 months, while continuing breastfeeding in terms of quality and quantity. Children should receive food with:
  - *Minimum food diversity* including 4 or more of following seven food groups: (1) Grains, roots and tubers, (2) legumes and nuts, (3) dairy products, (4) flesh foods (meat fish, poultry). (5) eggs, (6) vitamin A rich fruits and vegetables, and (7) other fruits and vegetables.
  - *Minimum meal frequency*, i.e. 2–3 times for breastfed infants 6–8 months; 3–4 times for breastfed children 9–23 months; 4–5 times for non-breastfed children aged 6–23 months, along with inter-meal snacks.
- **Active feeding for children during and after illness** should be encouraged except in medical contra-indications. In sick or depressed babies, expressed breast milk may be fed via nasogastric tube or cup and spoon. Use of infant feeding formula, even on donation or subsidized supply, should not be encouraged. Even in HIV infected mothers, exclusive breastfeeding is the default option for infant feeding, with opt-out option.
- **Responsive feeding,** i.e.: (a) recognition of early hunger cues given by the baby before crying for feeds, e.g. sucking movements/sounds, lip smacking, restlessness, etc, (b) encouraging the baby to feed himself/herself, (c) avoidance of forced feeding, and (d) psychosocial stimulation during feeding, e.g. playing or caressing the baby while feeding. Feeding should be an enjoyable experience for baby as well as the mother.

5.7 BALANCED DIET

Balanced diet is the *diet containing variety of foods in such quantities and proportions, which fulfils the needs for all essential nutrients, necessary to maintain optimal health, growth and reserves*.

Foods are conventionally grouped as: (a) cereals and millets, (b) pulses, legumes and nuts, (c) vegetables and fruits, (d) animal foods, e.g. milk, milk-products, eggs, fish, meat, etc. and (d) oils/fats and sugar.

Foods are also grouped according to predominant functions as: (a) energy-rich foods, i.e. carbohydrates and fats, (b) body-building foods, i.e. proteins, and (c) protective foods, i.e. vitamins and minerals.

Principles: General characteristics of a balanced diet, based on dietary goals from various sources *(prudent diet; WHO)* are as follows:

- *Quantitatively*, it should fulfil recommended daily allowances **(Table 5.1)** for all nutrients.
- *Qualitatively*, it should provide 15–20% of calories from proteins, 20–30% by fats* and rest 50–60% from carbohydrates, along with all desired micronutrients.

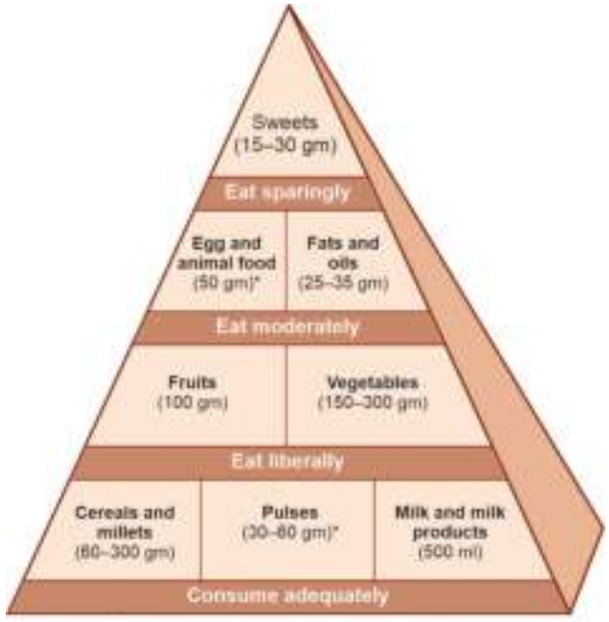
  *However, not more than 10% calories should be from saturated fats.
- It should contain adequate mix of different foodstuffs, e.g. cereals, pulses, vegetables, milk and other animal products, according to local dietary habits, customs and economic capacity.
- Various types of mixed diets include *Double mix* (cereals + pulses), *Triple mix* (cereals + pulses + vegetables) or *Quadri-mix* (cereals + pulses + vegetables+animal food). Cereal-pulse combination (*rice-dal, chapati-dal*) is a very rational dietary practice, as cereal proteins are deficient in lysine and pulse proteins in methionine. Consuming them together complements each other's amino acid deficiency to increase the nutritive value of food.
- Daily salt intake should not exceed >5 gm/day, though higher intake may be necessary in tropical countries, e.g. India.
- A balanced diet should also provide for adequate quality and quantity of other nutrients, e.g. vitamins and minerals, and *non-nutrients*, e.g. fibres, antioxidants and phytochemicals which bestow positive health benefits.
- It should be palatable, digestible and hygienic.
- Junk foods, e.g. colas, wafers, etc. should be restricted.

Food pyramid: Food pyramid is a graphic representation of the balanced diet with grossly recommended frequency and quantity of various food groups. It may vary according to the age, dietary habits and lifestyle **(Fig. 5.8)**.

Healthy plate or my plate concept, designed by the national institute of nutrition, Hyderabad is an easy to understand visual guide to display food from all food groups required in a healthy individuals plate, to ensure consumption of necessary nutrients in right quantity and right proportions, to prevent hidden hunger and protection from diseases.

5.8 NUTRITIONAL PROFILE OF INDIAN FOODS

Due to geographic variations in India, it is important to consider local food preferences, availability and affordability, while offering nutritional counseling. Nutritive values of common cooked ready-to-eat food items in Indian diet are given in **Table 5.9**. Nutritional values of common raw foods items are given in **Table 5.10**, though some important features are discussed here. All protein and caloric values in the following discussion are given as in 100 gm or ml of foodstuff, unless specified otherwise.



Based on: Dietary guidelines of Indians. National Institute of Nutrition 2011.

*Exchange 30 gm pulses with 50 gm of egg/fish/chicken/meat in non-vegetarians.

Figures in brackets denote approximate recommended intake for children 1–12 years (higher of the range for older children).

Fig. 5.8: Indian food pyramid (For children 1–12 years).

Cereals form the bulk of diet and contribute >70% and>50% of daily calories and protein intake, respectively. In general, cereals are rich sources of energy (300–350 cal), proteins (8–10 gm), vitamin B complex and minerals. However, *cereal proteins are deficient in lysine*.

- ***Rice*** is the staple food for over half of the world population. Although it contains less protein (7 gm %) than other cereals, rice protein is of better quality due to higher lysine content. Milling and cooking with excessive water significantly reduces its vitamin B complex content (present in its outer coating) which may be avoided by promoting the use of un-husked or *parboiled* rice. Thiamine deficiency, e.g. beri-beri is more common in rice-staple population.

  Parboiling is a process to preserve the nutritive value of rice by moving its vitamin content from outer coating to inner endosperm. It involves soaking the unhusked rice in hot water (65–70) for 3–4 hours, followed by steaming for 5–10 minutes, before drying and storing/milling.

TABLE 5.9: Nutritive values of ready-to-eat foods

Food items	*Cooked weight*/ number*	*Calories*	*Proteins (grams)*
Chapati (1)	25 gm	80	2.5
Paratha (1)	30 gm	170	2.5
Puri (2)	25 gm	90	2.5
Bread (1 slice)	30 gm	75	2.5
Dal/Sambar (1 katori)	100 gm	100	6
Poha/Upama (1 Katori)	50 gm	170	2
Corn flakes	50 gm	200	6
Idli/Vada (1 piece)	25 gm	100	5
Chicken/Mutton (1 Katori)	100 gm	200	18
Fish (2 pieces)	50 gm	190	2
Rice (1 katori)	25 gm	90	2
Khichri (1 katori)	25 gm	85	3
Daliya /Porridge (1 katori)	25 gm	80	2.5
Green veg (1 katori)	200 gm	50	4
Other Veg (1 katori)	200 gm	120	3
Milk (1 glass)	200 ml	150	6.5
Curd (1 cup)	100 ml	60	3
Biscuit (1)	5 gm	25	0.5
Egg (1)	45 gm	90	6
Banana (1)	Medium	70	0.5
Ghee/Oil (1 tsf)	5 ml	45	–
Sugar (1 tsf)	5 ml	20	–
Tea (1 cup)	150 ml	75	1.5
Coffee (1 cup)	150 ml	110	1

*Approximate values, may vary with cooking practices and size of utensils.
Standard size of utensils: Teaspoon: 5 ml, **Tablespoon:** 15 ml, **Cup/katori:** 200 ml, **Glass:** 250 ml.
Compiled from Dietary guidelines for Indians, National Institute of Nutrition 2011/2017 and other sources.

- ***Wheat,*** the second commonest staple cereal, is deficient in lysine and threonine. Whole grain wheat flour (aata) is more nutritious than white flour (maida), due to loss of vitamin B content during milling.
- ***Maize*** ranks third in world cereal consumption. Apart from lysine it is also deficient in *trytophan* – a niacin precursor, and *Pellagra* is common in maize-staple population. Some strains of maize also contain excess leucine that interferes with conversion of tryptophan to niacin in body.

Millets are smaller grains, e.g. jowar (sorghum), Bajra (pearl millet), ragi, etc., with caloric and protein value equal to cereals (except ragi). However, millet proteins are deficient in lysine and threonine.

Ragi, a low-cost popular millet provides less proteins (7 gm), but is a very rich source of calcium.

Pulses or Legumes include *Grams*, e.g. bengal-gram (Chana), green-gram (Moong), red-gram (Arher) and black-gram (Ural) and *beans*, e.g. soya bean and pea. All grams provide ~350 cal (equal to cereals), apart from proteins, vitamin B complex and minerals. Pulses are very rich sources of proteins (20–25 gm) in vegetarian diet, often termed as *poor man's meat*.

Nutritional value of pulses may be further enhanced by *germination* that increases vitamin B and C content. However, pulse-proteins are deficient in methionine and cysteine. In addition, uncooked pulses also contain some anti-nutrient factors, e.g. phytates and tannins, which inhibit absorption of other nutrients, e.g. iron.

- ***Soyabean*** is a very rich source of protein (42 gm), though deficient in methionine. Soya-milk is also used as infant feed during lactose intolerance.

Vegetables are considered as *protective foods* (along with fruits) due to their high vitamin and mineral content.

- ***Green leafy vegetables*** are essential in diet due to: (a) high vitamin B (except B_{12}), A and C content; (b) high iron and calcium content, (c) high fiber and water content, and (d) low caloric value (25–50 cal) with anti-obesity effect.
- ***Other vegetables***, e.g. potato, carrots, onion, radish, etc. are of limited nutritive value, except to increase palatability of diet. However, some of them are good sources of vitamins, e.g. carrot (vitamin A) or minerals, e.g. iron (radish, drum sticks). Roots and tubers, e.g. potato, sweat-potato and tapioca are rich in carbohydrates.

Fruits are valuable due to: (a) high vitamin content, e.g. vitamin A (papaya and mango), vitamin C (amla), (b) high mineral content, e.g. calcium (custard apple) and potassium (coconut water), (c) high caloric value, e.g. banana (100 cal), custard apple, etc., (d) high cellulose content (anti-constipating effect). *Dry fruits*, e.g. dates, raisins and apricot are rich sources of calories, iron and calcium.

Nuts and oilseeds, e.g. groundnut, coconut, mustard or sunflower seeds are rich sources of fats.

- ***Groundnut*** is a very rich source of calories (~550 cal) and proteins (25–30 gm), also called *poor man's cashewnut*. Even after oil extraction, groundnut flour retains its protein value and has been used to make supplementary foods, e.g. *balahar*.
- ***Dry nuts***, e.g. cashew nut, walnut, almonds, pistachio contain more fat than groundnut (35–65%), but less proteins. These nuts are good but costly source of minerals, e.g. calcium, phosphorus and iron.

Milk is the wholesome food for all ages, being rich and quality source of most nutrients. Breastfeeding is the best source of nutrition in early infancy. Other milks may be divided into two categories: (a) animal milk, (b) modified milk preparations, e.g. skimmed milk, toned milk, evaporated milk, dried milk powders, etc.

Animal milk: Composition of various animal milks differs significantly, as follows:

- *Cow milk* has a composition nearest to human milk with some differences **(Table 5.4)** and hence, commonly used for top feeding in infants, if necessary.

TABLE 5.10: Nutritive values of common Indian foods

Food Item (100 ml/gm)	*Calories (cal)*	*Proteins (gm)*	*Others*	*Food Item (100 ml/gm)*	*Calories (cal)*	*Proteins (gm)*	*Others*
Milk Products				**Non-veg**			
Human milk	65	1.1	F 3.4%	Eggs	168	13.1	–
Cow milk	73	3.3	F 4.4%	Mutton (Goat)	135	20.4	–
Buffalo milk	107	3.7	F 6.6%	Beef	137	22.6	–
Paneer	257	18.9	F ~15%	Pork	236	17.4	–
Curd	62	3.2	F 4.0%	Chicken	382	19.4	–
Cereals				Fish	~100–200	~15–20	–
Wheat	321	10.6	–	**Fruits**			
Rice	355	7.9	–	Mango	55	0.5	Vit A 2210 IU
Maize	333	8.8	–	Papaya	24	0.4	Vit. A 2740 IU
Millets				Orange	37	0.7	Vit A 2240 IU
Jowar	333	10	–	Apple	62.1	0.3	Iron 0.3 mg
Bajra	347	11	Ca 364 mg	Banana	110.2	1.3	–
Ragi	320	7.2	Ca 344 mg	Amla	58	0.5	Vit C 600 mg
Pulses				Guava	32.1	1.4	Vit C 212 mg
Bengal gram	328	21.6	–	**Vegetables**			
Green gram	325	23.9	–	Potato	70	1.5	–
Red gram	335	21.7	–	Onion	48	1.5	–
Black gram	323	23.1	–	Tomato	19	0.8	–
Beans				Carrot	38	1.0	Vit A 1167 IU
Soya bean	376	37.8	–	Radish	31	0.8	–
Red-beans	298	19.9	–	Leafy veg	20–30	1.5–3.5	Vit B +++
Lentils	315	22.5	–	Other veg	15–25	1.5–2.5	Fibres ++
Nuts and seeds				**Fats and oils**			
Ground nut	518	23.7	F 39.6%	Ghee/Oils	900	–	F100%
Coconut (fresh)	407	3.8	F41.4%	Butter	729	–	F 81%
Cashewnut	580	18.8	F 45.2%	**Sugars**			
Walnut	669	14.9	F 64.3%	Cane sugar	398	0.1	–
				Jaggery	352	1.9	–

*Source: Indian food composition tables, National Institute of Nutrition, 2017, **F:** Fat*

- *Buffalo milk* has very high fat and caloric content and hence, should be used only after proper dilution, especially in infancy.
- *Goat milk*, though better digestible than the cow milk (less curd formation), is deficient in folic acid (megaloblastic anemia) and carries additional risk of causing brucellosis, if used without boiling.

As animal milk is regularly contaminated, boiling is essential before consumption. Currently all marketed milks are pasteurized for this purpose.

Pasteurization involves heating of raw milk at 63 for 30 minutes (or 72 for 15 seconds) followed by rapid cooling, to eliminate all pathogenic bacteria and reduce non-pathogenic bacterial count <50,000/ml. Pasteurization also improves digestibility of casein with less curd formation.

Modified milk preparations include:

- *Skimmed milk* is available in liquid and dried form (milk powders), prepared after removing most of the cream from animal milk, with fat content of 0.5% in full-skimmed milk or 1.5% in half-skimmed milk.
- *Toned milk*, cheapest milk, is prepared by mixing natural milk, water and milk powder (1:1:8) followed by pasteurization before packaging. It has composition similar to cow milk.
- *Evaporated milks* are commercial available as concentrated milk in liquid form, with long shelf-life for many months.

Skimmed milk and evaporated milk should not be used for infant feeding due to high protein and mineral content that may cause dehydration. However, these milks are useful as a dietary supplement for older children during fresh milk shortage.

Commercial milk formulas, modified according to the age-related requirements and fortified with various nutrients are available for top feeding, though costly and require careful reconstitution.

Eggs are known for their quality protein content (6 gm/egg), containing all essential amino acids. Egg protein is considered as ideal or *reference protein* (NPU ~96), with whom other proteins are compared. Milk and meat protein has an NPU of 75 and 80 respectively, while vegetable proteins have even lower NPU, i.e. ~ 60–65%.

Boiled egg is better than raw egg as boiling destroys *avidin*—a substance that prevents biotin absorption. Eggs

are also rich sources of energy (70 cal), vitamins (except vitamin C) and minerals.

Sea-foods including fishes, are rich in quality proteins (15–25 gm%), unsaturated fatty acids, fat-soluble vitamins and minerals, e.g. calcium, phosphorus and fluorine. Sea fish/foods also contain iodine, which is deficient in fresh-water fishes. However, fish contains very little carbohydrates.

Meat and animal organs, e.g. liver, are good sources of quality proteins (15–20 gm%), vitamins, e.g. vitamin D and B complex, minerals, e.g. iron, zinc (but deficient in calcium).

Fats and oils are good sources of energy (9 cal/gm) and increase palatability of diet.

- ***Vegetable oils*** are rich in EFA and PUFA (except coconut and palm oil), but contain little vitamins A and D, unless fortified (vanaspati ghee). High PUFA content in vegetable oils limits hypercholesterolemia, obesity and consequent health problems. *Coconut oil* is rich in triglycerides, which is absorbed directly without *micelles* formation (bile-based absorption) and hence, useful source of energy in preterms and chronic liver disease.
- ***Animal fats*** lack EFA and mainly contain saturated fatty acids with obesity-effect. However, animal fats are useful source of energy in malnourished children and contain plenty of fat-soluble vitamins.

Other food products, e.g. sugar, condiments/spices and beverages have very limited dietary value, except to increase its palatability.

5.9 NUTRITIONAL ASSESSMENT

Nutritional assessment is a vital component of child health examination, not only to detect early undernutrition but also to plan appropriate counseling and interventional strategies. While often used interchangeably, term *nutritional assessment* and *dietary assessment* have different connotations.

Dietary assessment denotes assessment of actual dietary intake by the child as compared to recommended dietary allowances for the age and gender to identify the deficit/s, if any.

Nutritional assessment is a broader term to encompass dietary assessment as well as assessment of the nutritional status in terms of anthropometric, clinical and biochemical parameters to identify presence of clinical or subclinical nutritional deficiencies, which may or may not be due to dietary causes.

Nutritional assessment is a comprehensive process, involving:

- *Dietary assessment*, generally based on the 24-hours dietary-recall method. Other methods of dietary assessment, e.g. *diary method* or *replicate diet* are rarely used in clinical practice.
- *Anthropometric assessment* by recording body measurements, e.g. weight, height and mid-upper arm circumference and comparing them with age/gender related norms to identify growth delay, the most common consequence of nutritional deficiencies.
- *Clinical assessment* for signs of macronutrient or micronutrient deficiencies.
- *Biochemical assessment* in selected cases to confirm presence of suspected nutrient deficiencies.

A. Dietary assessment: Dietary history must be relevant to the age, though basic information about early infant feeding (breast/top feeding) and complimentary feeding should be recorded in all cases. Important aspects of dietary history are as follows:

- *In infants < 6 months*, dietary history must concentrate on the type of feeding, e.g. breast/top feeding, appropriateness of breastfeeding practices, problems encountered during breastfeeding, reasons for initiating top-feeding, appropriateness of top feeding, if practiced.
- *In children from 6 months-2 years*, dietary history must focus on complimentary feeding along with a quick review of early infant feeding, with special emphasis on *age* of introducing complementary feeds, *adequacy* of these feeds in terms of quality (minimum dietary diversity) and quantity (minimum meal frequency), and *problems* encountered during complementary feeding. It should also record whether the breast-feeding has been continued.
- *In children > 2 years*, dietary history should concentrate on the current food intake apart from quick review of the early infant feeding and complementary feeding.

In clinical practice, dietary intake is usually calculated by *dietary recall method*, by:

- Asking the mother to recall daily consumption of different food items during last few days before the onset of present illness,
- Calculating the average daily intake of nutrients, mainly energy and proteins using known nutritional value of common Indian feeds **(Tables 5.9 and 5.10)**, and
- Then comparing this calculated intake with reference nutritional requirements for the chronological age, **(Table 5.1)**, to find out the deficit/s, if any.

Other methods to assess dietary intake, e.g. *diary method* or *replicate diet method are used only for research purpose.*

B. Anthropometric assessment: Three anthropometric indices are commonly used for regular nutritional assessment–weight, length/height and mid upper-arm circumference or MUAC (in children < 5 years), which should then be compared with age-related reference values (Ch 2.5).

Age-independent parameters, *e.g.* are useful when the exact chronological age of child is in doubt. These

TABLE 5.11: WHO classification for undernutrition

Underweight	WFA <-2SDS	Severe underweight	WFA <-3SDS
Stunting	HFA <-2SDS	Severe stunting	HFA <-3 SDS
Wasting	WFH <-2SDS	Severe wasting	WFH <-3SDS

WFA: Weight for age; **HFA:** Height for age; **WFH:** Weight for height; **SDS:** Standard deviation score

parameters are derived by comparing the relationship between two age-related parameters—one *early* indicator, e.g. weight and other *late* indicator, e.g. height. *Weight for height is the* commonly used age-independent indicator of undernutrition.

While weight is an early indicator of nutritional faltering (*wasting*), height is not be affected for many months and hence considered as an indicator of long-term nutritional deprivation (*stunting*). Based on anthropometric data, child may be classified as normal, wasted, stunted or wasted and stunted, with different grades of severity as per WHO classification **(Table 5.11)**.

Screening tests are simple, inexpensive tools used in large nutritional surveys of pre-school children, usually based on MUAC, which is fairly consistent between 1–5 years of age. Commonly used screening test include:

- *Shakir's tape*, a special plastic tape with three color zones-green, yellow and red, each representing MUAC of >13.5 cm, 12.5–13.5 cm, and <12.5 cm respectively. When applied on the mid-arm, green zone indicates normal nutrition, yellow zone warns borderline PEM and red zone indicates severe malnutrition.
- *Bangle test* uses a bangle with inner diameter of 4 cm. When slipped over the forearm, if it crosses the elbow, malnutrition is present.

C. Clinical assessment involves thorough physical examination and search for warning signs for nutritional deficiencies, if present. While it is the simplest method to search for nutritional deficiencies, drawbacks include: (a) sub-clinical deficiencies can be missed, (b) quantification of the severity may be difficult, and (c) nutritional deficiencies with common clinical presentations may not be precisely identified, e.g. *xerosis* may be due to vitamin A or essential fatty acid deficiency, or *pallor* may be due to iron or folic acid deficiency.

D. Biochemical assessment is indicated only in selected cases to confirm the presence of selective nutrient deficiency or to identify subclinical deficiencies, if necessary for the purpose of early diagnosis and treatment. Relevant biochemical tests to detect subclinical nutritional deficiencies have been discussed in respective chapters (Ch 6.1–6.7).

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CHAPTER

6

Nutritional Disorders

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6.1 CHILDHOOD UNDERNUTRITION

Undernutrition refers to a *range of pathological conditions arising from the coincidental lack in varying proportions of proteins and calories.* Children are more vulnerable to undernutrition due to relatively higher caloric and protein requirements for growth and physical activity.

Prevalence: While rarely a presenting illness by itself, undernutrition is an underlying problem in over half of morbidity and mortality in under-five Indian children.

Epidemiologically, the prevalence of undernutrition is generally assessed and reported in under-five children on the basis of WHO criteria **(Table 5.11)**. Recent NFHS-V data (2020–21) suggests that on all India basis:

- Overall prevalence of *underweight* in under-five children is 32.1%.
- Chronic undernutrition, i.e. *stunting* is more common (35.5%) than acute malnutrition, i.e. *wasting*, (19.3%).
- While the prevalence of underweight, wasting and stunting has marginally declined in recent years, severe wasting continues to be as common, if not more, as in NFHS-IV (2015–16), i.e. 7.7% vs 7.5%.
- Prevalence of undernutrition is much higher in girls, low socioeconomic status, rural children and in underdeveloped BIMARU states, e.g. Bihar, Madhya Pradesh, Rajasthan and Uttar Pradesh.

6.1.1 ETIOPATHOGENESIS

Undernutrition is a result of complex interplay between: (a) *inadequate dietary intake,* due to various dietary, socioeconomic and cultural factors, and (b) *increased nutritional requirements,* due to infections or illnesses. Common etiological factors, associated with undernutrition include:

- ***Child-related factors:***
  - Low birth weight
  - Absence or early cessation of breastfeeding
  - Delayed or inappropriate complementary feeding
  - Incorrect dietary habits, e.g. *food fads and junk foods.*
  - Recurrent infections, e.g. diarrhea, respiratory infections, measles, helminthiasis, etc.
- ***Maternal factors:***
  - Lactation failure
  - Maternal malnutrition/illnesses
  - Ignorance about child-feeding practices
  - Separation, e.g. dead, single or working mother
- ***Socioeconomic factors:***
  - Poverty and unemployment
  - Large family size
  - Unhygienic living conditions
  - Inequitable food distribution in family, with mothers and infants being last priority
  - Disadvantaged children, e.g. girls, orphans, etc.
- ***Cultural factors:***
  - *Wrong beliefs,* e.g. colostrum is harmful, hot/cold foods to be avoided in children, milk aggravates diarrhea, etc.
  - *Wrong customs,* e.g. delayed introduction of complementary feeds, waiting for religious ceremonies (annaprashan).
  - *Wrong cooking practices,* e.g. peeling of vegetables before cooking, use of polished food, draining away the water after cooking, etc.
- ***Community factors:***
  - Natural/man-made disasters with food shortage, e.g. famines, wars, civil unrests.
  - Inappropriate agricultural practices, production and distribution of food grains.
  - Generalized economic depression.
  - Inadequate primary health care.

It is not yet clear, why some malnourished children clinically present differently from others (marasmus *vs* kwashiorkor).Various theories have been suggested to explain different clinical presentations in PEM, of which two are important and deserve mention here

a. **Adaptation theory** suggests that during early stages of nutritional deficiency, human body tries to adapt by: (a) curtailing energy expenditure by reduced physical activity and growth, (b) efficient utilization of available calories by enhanced glucose uptake by

cells, and (c) utilizing endogenous stores, e.g. muscle proteins and subcutaneous fat via neoglucogenesis. However, these adaptive mechanisms require many metabolic and hormonal changes and their success depends on the availability of enough time and endogenous resources.

Children with *gradual nutritional deprivation*, e.g. delayed or inappropriate complementary feeding adapt better and develop marasmus-like illness with growth failure, muscle wasting and loss of subcutaneous tissue. Lack of urgency for endogenous catabolism as well as limited muscle mass and hepatic stores in them prevent development of edema and hepatomegaly.

Conversely children with *sudden nutritional deprivation*, e.g. those with acute illnesses or infections get less time is available to adjust for lower energy intake, necessitating rapid mobilization of endogenous stores (neoglucogenesis), leading to kwashiorkor-like state with edema (due to protein utilization) and fatty hepatomegaly (due to lipolysis).

b. **Role of infections:** Infections and nutrition are closely linked to each other **(Fig. 6.1)** and infections, e.g. diarrhea, acute respiratory infections or measles, are common preceding events to precipitate malnutrition in sub-clinically undernourished children, due to sudden widening of demand–supply gap. Kwashiorkor is relatively more common following infections than marasmus, due to inadequate adaptation.

6.1.2 CLINICAL SPECTRUM

Clinical spectrum of undernutrition is a *continuum*, ranging from borderline growth delay to well-defined syndromes of marasmus or kwashiorkor. Within this spectrum, many other terms are also used to denote clinical variations, e.g. pre-kwashiorkor, marasmic kwashiorkor, nutritional dwarfism, etc.

Kwashiorkor, a term coined by Prof. Cicely Williams, denotes acute PEM due to either sudden nutritional deprivation, e.g. abrupt cessation of breastfeeding (*deposed child*) or sudden increase in nutritional requirements due to infection, diarrhea, etc. *Moderate weight loss (61–80%), edema and mental changes are three cardinal features of kwashiorkor,* usually but not invariably, associated with hepatomegaly, skin/hair changes, vitamin deficiencies, etc.

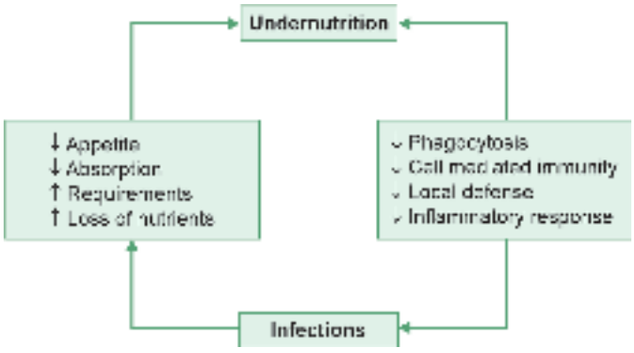


Fig. 6.1: Undernutrition and infection interaction.

Marasmus, a term derived from Greek word *marasmos* (wasting), is a state of chronic and severe undernutrition due to gradual nutritional deprivation, e.g. delayed complementary feeding with widening gap between nutritional requirements and breast milk output. *Severe weight loss (<60%), wasting of muscles and subcutaneous tissue and absence of edema are hallmark of marasmus.*

Some important clinical features of undernutrition with differences between kwashiorkor and marasmus are as follows **(Table 6.1)**:

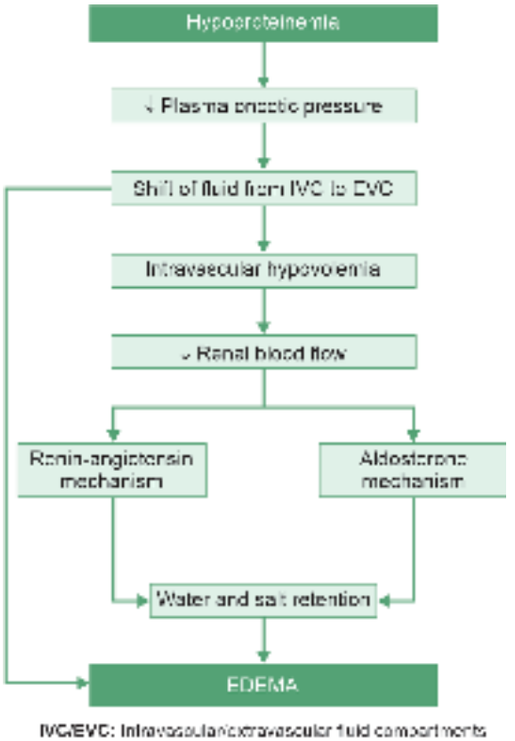
- ***Growth failure:*** Wasting is the essential feature in all malnourished children with/without stunting, more obvious in marasmus due to absence of edema. A marasmic child has typical shriveled (*monkey like*) look with gross emaciation, relatively larger head, staring eyes, prominent ribs, wrinkled skin and loose skin-folds over buttocks, inner thighs, axilla and chest. Buccal pad of fat is usually preserved except in severe marasmus **(Fig. 6.2)**. Bone age and dentition may also be marginally delayed.
- ***Edema*** is the *sine qua non* of kwashiorkor, due to hypoproteinemia and consequent fluid retention **(Fig. 6.3)**, though severity may vary from mild pitting edema over dependent parts, e.g. legs or sacrum, to generalized anasarca **(Fig. 6.4)**. Severe edema may mask underlying wasting, weight loss and dehydration.

TABLE 6.1: D/D kwashiorkor *vs* marasmus

		Kwashiorkor	***Marasmus***
1.	Age	>1 year	Any
2.	Dietary history	Early cessation of breastfeeding	Delayed
3.	Onset	Acute	Gradual
4.	History of infection	Frequent	Uncommon
5.	Edema	Essential	Absent
6.	Growth failure a. Weight b. Height c. Wasting	 60–80% N/↓ +, masked	 <60% ↓↓↓ +++
7.	Mental changes	Apathetic	Alert
8.	Appetite	Poor	Good
9.	Skin/hair changes	Common	Rare
10.	Hepatomegaly	Present	Uncommon
11.	Vitamin deficiencies	Common	Masked
12.	Hypoproteinemia	++/+++	+

Fig. 6.2: Clinical appearance of PEM (Marasmus).

Fig. 6.4: Clinical appearance of PEM (Kwashiorkor).



IVC/EVC: Intravascular/extravascular fluid compartments

Fig. 6.3: Pathogenesis of edema in kwashiorkor.

Fig. 6.5: (A) Crazy pavement dermatosis, (B) Flaky-paint dermatosis.

- ***Mental changes:*** Children are typically apathetic and lethargic in kwashiorkor with little interest in surroundings, probably due to impaired activity of CNS enzymes in an *un-adapted* child. Anorexia is also marked in these cases. In contrast, marasmic children have good appetite and are usually alert with roving eyes as if searching for food.
- ***Skin changes*** are more pronounced in kwashiorkor than marasmus due to combined effect of: edema, multiple vitamin deficiencies, essential fatty acid deficiency and secondary infections. Depending on the severity, these changes include: (a) *phrynoderma*, i.e. generalized dryness of skin, (b) diffuse or patchy areas of hypo/hyper pigmentation, (c) thin, shiny, taut skin over edematous areas, (d) moist ulcerations over flexural areas or pressure points, (e) superadded infections, e.g. pyoderma and scabies. Following lesions are classical but uncommon except in severe kwashiorkor **(Fig. 6.5A and B)**:
  - *Flaky paint dermatosis,* i.e. hyperpigmented and desquamating area (*flakes)* over raw-skin;
  - *Crazy pavement dermatosis,* i.e. hyperkeratotic, fissured skin with alternate areas of hypo-or hyper-pigmentation;
  - *Mosaic dermatosis* with mixed lesions in mosaic form.
- ***Hair changes*** are more common in kwashiorkor with thin, dry, sparse, lusterless, hypopigmented and

easily pluckable hair. Due to intermittent periods of better nutrition, alternate bands of hypo-and normal pigmentation on hair are classically described as *flag sign.* In marasmus, hair are sparse and hypopigmented.

- ***Hepatomegaly*** is common in kwashiorkor due to fatty infiltration of liver, though jaundice is rare and indicates poor prognosis.
- ***Concomitant nutritional deficiencies*** like xerophthalmia, vitamin B complex deficiencies, scurvy and anemia are more obvious in kwashiorkor. Although biochemical vitamin/mineral deficiencies are common in marasmus as well, clinical signs are less prominent in them due to adaptive mechanisms and usually appear in recovery phase.

  Anemia in PEM is usually dimorphic, due to: (a) reduced dietary intake of hemopoietic factors like iron, proteins and folic acid, (b) co-existing infections affecting erythropoiesis, and (c) occult blood losses due to worm infestations.
- ***Concomitant infections*** like intermittent episodes of diarrhea, respiratory infections and skin infections are common in PEM, due to impaired immune mechanisms **(Fig. 6.1)** and mucosal integrity. *Cellular immunity and phagocytic functions are predominantly affected in PEM, while immunoglobulin levels are usually normal or high with good antibody response.*

  Presence of infections may be clinically masked in undernutrition due to poor inflammatory responses, e.g. fever and leukocytosis. Hypothermia is an important indicator of infection in these children. Diarrhea in PEM may also result from malabsorption due to intestinal villous atrophy and consequent lactase deficiency, as well as due to hepatic/pancreatic dysfunction.

6.1.3 DIAGNOSTIC ASSESSMENT

Assessment of a child with undernutrition involves: (I) assessment of dietary intake, (II) assessment of nutritional status, (III) classification of severity, and (IV) identification of complications.

I. Assessment of dietary intake is the first step in screening for undernutrtion, already discussed in chapter on nutritional assessment (Ch 5.9). It includes history of age-related infant and young child feeding (IYCF) practices, e.g. breastfeeding and complementary feeding as well as assessment of the actual dietary intake before the onset of presenting illness, usually by *dietary recall method*.

II. Assessment of nutritional status on the basis of anthropometric, clinical and biochemical parameters, as follows:

- ***Anthropometric parameters*** may be broadly divided into: (i) age-dependent parameters or (ii) age-independent parameters.

  Age-dependent parameters, e.g. weight and height are two most commonly used anthropometric indicators of undernutrition. *Weight* is the first anthropometric parameter to decrease in undernutrition and hence, considered as an indicator of acute malnutrition. Height is affected only after many months of undernutrition and hence, considered as indicator of the chronic undernutrition.

  Age-independent parameters are useful when the exact chronological age of child is in doubt and are derived by comparing the relationship between two age-related parameters-one *early* indicator, e.g. weight and other *late* indicator, e.g. height. Weight for height is the most commonly used age-independent anthropometric parameter in assessment of undernutrition. However, it may be misleading in chronic cases due to proportionate fall in weight as well as height. Other rarely used age-independent indicators include: mid upper arm circumference or MUAC (for children aged 1–5 years only), Kanawati Index (MUAC/head circumference) and skin fold thickness.

  Screening parameters are simple, inexpensive tools for mass nutritional surveillance of preschool children including Shakir's tape or Bangle test (Ch 5.9).
- ***Clinical diagnosis*** depends on the features discussed earlier in Ch 6.1.2, though with following caveats:

  Edema shall be considered as a clinical sign of undernutrition only if it is bilateral and has no other known etiology, e.g. nephrotic syndrome.

  Wasting as an indicator of growth failure is a subjective sign and should be used only if anthropometric parameters are no available or feasible. It may be masked in children with edema (kwashiorkor) or may be more marked in those with associated severe dehydration.
- ***Biochemical parameters*** are rarely used in clinical practice, mainly useful to detect early sub-clinical cases of undernutrition. Earliest biochemical change in undernutrition is the decrease in essential amino acid (EAA) levels—which cannot be synthesized endogenously, leading to altered EAA/non-EAA ratio in plasma. Subsequently, plasma albumin levels fall, though the edema appears only when plasma albumin levels drop < 2.5 gm/dl.

III. Classification of severity: Various classifications systems were in vogue earlier, to denote severity and duration of PEM, as follows:

- *Weight for age (WFA) based classifications*, are simple and commonly used in practice, though do not indicate the duration of malnutrition and include *Indian Academy of Pediatrics classification* **(Table 6.2)**, *Gomez classification, Jellife's classification, etc.*
- *Height/length-for-age (HFA) based classifications* are rarely used in practice and included *Waterlow's classification or McLaren's classification, etc.*

TABLE 6.2: Indian Academy of Pediatrics (IAP) classification

*Weight for age**	*Nutritional status**
>80%	Normal
71%–80%	Grade I PEM
61%–80%	Grade II PEM
51%–60%	Grade III PEM
<50%	Grade IV PEM

*As compared to 50th percentile of normal

TABLE 6.3: Welcome-trust classification

*Weight for age**	*Edema*	*Type of PEM*
80–60%	Absent	Undernutrition
	Present	Kwashiorkor
<60%	Absent	Marasmus
	Present	Marasmic kwashiorkor

*As compared to 50th percentile of normal

- *Composite classifications*, based on anthropometric as well as clinical criteria, are most informative and include *Welcome-trust classification* **(Table 6.3)**, *Waterlow's classification, WHO classification, IMNCI classification, etc.*

  WHO classification, most widely used classification for epidemiological purpose rests on two anthropometric parameters: (a) weight for height (WFH) as a measure of acute malnutrition, and (b) height for age (HFA) as a measure of chronic malnutrition, along with one clinical parameter, i.e. presence of symmetrical *edema*. It classifies all undernourished children in two major categories – moderate malnutrition and severe malnutrition, with each category further sub-divided as wasted and stunted (if WFH and HFA is between 2–3 SD respectively) or severely wasted or severely stunted (if WFA and HFA are < 3SD respectively). All cases with edema are considered as having severe malnutrition **(Table 6.4)**.

  IMNCI classify nutritional status in children from 2 months to 5 years of age as: (a) severe acute malnutrition with complications, (b) severe acute malnutrition without complications, (c) moderate acute malnutrition, and (d) no acute malnutrition **(Table 6.5)**.

IV. Assessment of complications: Malnutrition is rarely a primary cause of hospital visit, often presenting with complications **(Table 6.6)** with significant impact on the morbidity and mortality. Identification of these complications is also important to decide the need of hospitalization and strategies of management.

V. Investigations: Although PEM is a clinical diagnosis, following investigations are required on admission (initial assessment), to exclude or identify complications.

- Complete hemogram including peripheral smear for anemia and infections (malaria).

TABLE 6.4: WHO classification for undernutrition

	Moderate undernutrition	*Severe undernutrition*
Edema	No	Yes Edematous malnutrition
Wt for Ht (Z-score*)	– 2 to – 3 Wasting	< – 3 Severe wasting
Ht for age (Z-score*)	– 2 to – 3 Stunting	< – 3 Severe stunting

*or SD score

TABLE 6.5: IMNCI classification for malnutrition

a.	**Severe acute malnutrition with complications** WFL/H <-3SDS *or* MUAC<11.5 cm *or* bilateral pedal edema **And** medical complications*
b.	**Severe acute malnutrition without complications** WFL/H <-3SDS or MUAC<11.5 cm or bilateral pedal edema **And** No medical complications
c.	**Moderate acute malnutrition** WFL/H <-2 to-3SDS or MUAC<11.5-12.4 cm
D.	**No acute malnutrition** WFL/H >-2 SDS or MUAC<12.5 cm

WFL/H: Weight for length/height, **MUAC**: Mid-upper arm circumference
*Medical complications include (a) any general danger sign, (b) any severe classification, (c) pneumonia, (d) diarrhea with dehydration, (e) poor appetite.

TABLE 6.6: Complications of PEM

Early (presenting) complications		
a.	Infections	
	Common	: ARI, diarrhea, TB, helminthiasis
	Severe	: Gram –ve sepsis, septic shock, DIC
	Opportunistic	: Candidiasis
b.	Hypothermia	
c.	Metabolic	
	Hypoglycemia	
	Hypocalcaemia	
	Hypomagnesemia	
d.	Fluid and electrolyte imbalance	
	Dehydration	
	Hypokalemia	
	Hypernatremia	
e.	Lactose intolerance	
f.	Severe anemia and other nutrient deficiencies	
g.	Congestive cardiac failure	
Late (recovery) complications		
a.	Diarrhea (lactose intolerance)	
b.	CCF (high protein and solute diet)	
c.	Unmasking of subclinical vitamin/mineral deficiencies	
d.	Recovery syndromes (*see* text)	
Long-term effects		
a.	Growth retardation	
b.	Cognitive and learning disabilities	

- Urine examination, specially for pus cells (UTI),
- Stool examination, specially for fat globules (malabsorption),reducing sugars (lactose intolerance) and microscopic ova/cysts,
- Chest skiagram for tuberculosis, respiratory infections,
- Tuberculin test, which may be false negative in severe PEM due to impaired cell mediated immunity.
- Biochemical tests, specially: S. albumin (hypoproteinemia) blood sugar (hypoglycemia) S. electrolytes (Na^+, K^+, Ca^{++} and Mg^{++}) and liver/renal function tests,
- Microbial cultures (blood, urine, others),
- Other relevant investigations.

6.1.4 SEVERE AND MODERATE ACUTE MALNUTRITION (SAM AND MAM)

While chronic malnutrition is more common, children with acute malnutrition are at highest risk of death and serious complications, who need immediate medical attention.

Hence, for the purpose of management, WHO/UNICEF in recent years has categorized acute malnutrition as *severe acute malnutrition* (SAM) and *moderate acute malnutrition* (MAM), to standardize management strategies **(Table 6.7)**.

Severe acute malnutrition *(SAM)* is defined as presence of *any one* of the following criteria in children 6 months to 5 years:

- Weight for length/height < – 3 SDS or z-score,
- Mid-upper arm circumference <11.5 cm,
- Presence of bilateral pedal edema.

In addition, IAP guidelines also include *visible wasting* as an additional criteria for SAM, though it is highly subjective and should be used only if: (a) anthropometric parameters, e.g. Wt, Ht and MUAC are not available; or (b) length is <45 cm, as weight for length charts are not available for children measuring <45 cm.

Moderate acute malnutrition *(MAM)* is defined as presence of *any one* of the following criteria in children 6 months to 5 years:

- Weight for length/height between –2 and –3 SDS or z-score,
- Mid-upper arm circumference between 12.4 cm to 11.5 cm.

TABLE 6.7: Diagnostic criteria for SAM and MAM in children

	6 mo-5 yr	*< 6 mo*	*MAM*
Wt for L/Ht	< 3 SD	< 3 SD	–2 to –3 SD
MUAC	<11.5 cm	NA	12.4–11.5 cm
Bilateral edema	present	Present	Absent
Visible wasting	NA	Present	Absent

MUAC: Mid-upper arm circumference

In children below 6 months, same criteria may be used for diagnosis of SAM and MAM except MUAC and including those with visible wasting as SAM.

6.1.5 MANAGEMENT OF SEVERE ACUTE MALNUTRITION

SAM is a major cause of mortality and morbidity and needs specialized care in a hospital or *nutrition rehabilitation centers (NRC)* – dedicated units in hospitals for nutritional therapy and support. However, some cases of SAM do not need hospital care and may be managed at home under supervised care. Thus, the management of SAM may be broadly divided into: (a) facility-based care, and (b) community-based care, discussed in the following sections.

A. Facility-based Care

Hospitalization is indicated in all cases of SAM (6–59 months) *with* following risk factors:

- Complicated SAM with life-threatening complications, i.e. infections, hypothermia, dehydration, electrolyte/metabolic derangements, severe anemia, etc. **(Table 6.6)**.
- Presence of severe edema
- Presence of danger signs of IMNCI (convulsions, altered sensorium, inability to drink/feed, persistent vomiting)
- Failure to pass appetite test
- Lack of reliable home care/supervision

In addition, *all infants <6 months with SAM and/or those who are too weak or feeble to suckle*, need hospitalization.

Appetite test aims to assess the extent of the loss of appetite. Children with good appetite, even with SAM, can be managed on outdoor basis in absence of other complications. It involves offering the child a measured amount of feed and assessing the unconsumed portion to calculate the intake.

- *For children 7–12 months*: Offer 30–35 ml/kg of catch-up formula diet **(Table 6.11)**. Child is considered to have good appetite, if she/he can consume >25 ml/kg.
- *For children >12 months*: Offer a specially prepared feed from local ingredients (mix *roasted and grinded groundnut 1000 gm, grinded sugar 1120 gm, milk powder 1200 gm and coconut oil 600 gm* and store in air-tight container in refrigerator; to be used within one week).

To pass the appetite test (good appetite), child should be able to consume >15 gm (wt <4 kg), >25 gm (wt 4–7 kg) and >33 gm (7–10 kg) of this feed.

Appetite test should be performed in a separate quiet area after explaining the purpose and procedure to the mother. The child should not have been fed in last two hours and must not be forced to take the feed. The test may take up to one hour and the remaining amount must be measured to assess the intake.

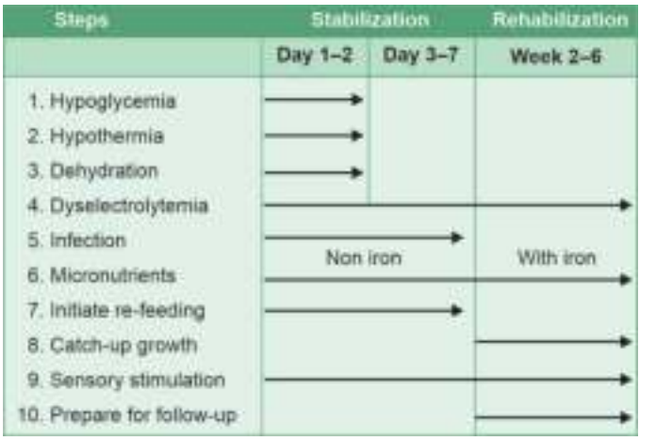


Fig. 6.6: Ten steps in management of SAM (WHO).

Ten steps of SAM management: Management of SAM may be broadly divided into three phases: (a) stabilization phase, (b) transition phase, and (c) rehabilitative phase.

- *Stabilization phase (1–2 days)* involves treatment of major medical complications and initiation of re-feeding with suitable starter feeds to promote normalization of metabolic function and nutrition-electrolytic balance.
- *Transition phase (2–3 days)* after stabilization, aims to ensure that the child is clinically stable before gradual switch-over from starter diet to catch-up diet.
- *Rehabilitation phase (2–6 weeks)* aims to promote rapid weight gain, stimulate emotional and physical development and prepare the child for discharge, after gradual switch-over on home diet.

WHO has proposed 10 essential steps in the management of SAM within a given timeframe **(Fig. 6.6)**, as follows:

Step I. Treat and prevent hypoglycemia: All SAM children are at risk of hypoglycemia (blood glucose <54 mg/dl) and should be checked for blood glucose levels on admission. If it is not possible, hypoglycemia must be assumed to be present.

Asymptomatic hypoglycemia is more common and should be treated promptly by 50 ml of 10% dextrose/sugar solution, fed orally or via nasogastric tube, followed by the first feed of starter F-75 formula (discussed later, **Table 6.9**) every two hours to prevent recurrence. First F-75 feed may be given as small volume ($1/4^{th}$ part of 2-hourly feeds) every 30 minutes, till the stabilization. blood glucose levels should be re-checked 2-hrly, till stabilized.

Symptomatic hypoglycemia with altered sensorium and/or seizures, should be treated promptly with IV dextrose 10% (5 ml/kg) as bolus, followed by oral dextrose/sugar solution or F-75 feed, as discussed earlier for asymptomatic hypoglycemia. Blood glucose levels should be rechecked 2-hourly, till stabilized.

Hypoglycemia can be prevented by frequent regular feeds, including at night along with periodic monitoring.

Step II. Treat and prevent hypothermia: Hypothermia (rectal temperature <35.5°C) is more common in marasmus due to less subcutaneous fat. It may also indicate underlying hypoglycemia or infections. Blood glucose levels should be checked in all cases of hypothermia. Baby should be assumed as hypothermic, if rectal thermometer is not available and temperature is not recordable by skin thermometer.

Treatment of hypothermia involves: (a) gradual re-warming under radiant warmer/blanket or putting him/her on the mother's bare chest for skin-to-skin contact, (b) frequent feeding, and (c) starting antibiotics as per step V. Rectal temperature should be monitored every 30 minutes, till it exceeds 36.5°C.

Prevention of hypothermia involves: (a) frequent 2-hourly feeding even during nights, (b) keeping the baby warm and well covered with mother and dry by changing wet-nappies as needed, and (c) avoiding prolonged cold-exposure for examination or procedures.

Step III. Treat and prevent dehydration: Dehydration is common in malnourished children due to co-existent diarrhea/vomiting, poor oral intake and redistribution of body fluids. Severity of the dehydration is often overestimated in these cases and parenteral fluids should be avoided unless the patient is in shock. Conversely, dehydration may be missed in edematous children. Any SAM child with diarrhea must be presumed as dehydrated.

Mild to moderate dehydration is preferably treated with WHO-ORS, given orally or via nasogastric tube as 5 ml/kg every 30 minutes for first two hours, followed by 5–10 ml/kg/hr for maximum 12 hours, depending on the needs. While IAP recommends use of WHO-ORS for this purpose, WHO recommends use of half-diluted ORS or ***Re**hydration **So**lution for **Mal**nutrition* (ReSoMal) to rehydrate SAM children, except in cases of cholera or profuse watery diarrhea.

ReSoMal, though rarely used, can be prepared by diluting one packet of WHO-ORS in 2 liters of water (instead of 1 liter) and adding 50 gm of sugar and 40 ml of specially prepared electrolyte-mineral solution. It should be used only under medical supervision in in-patient care.

All cases should be monitored for hydration by pulse rate, respiratory rate, urine output and stool/vomit frequency, every 30 minutes in first two hours and then hourly for next 6–12 hours. Oral fluids must be replaced with F-75 feeds in the same volume at 4, 6, 8 and 10 hours, if dehydration continues.

Parenteral fluid therapy is necessary in cases with shock, with a cautious approach due to risk of fluid overload. IV Ringer lactate or N/2 Saline in DW 5% is

preferred, given as 15 ml/kg in first hour and repeated after one hour (in responders), followed by switch-over to oral fluids. All cases should be closely monitored for signs of fluid overload, e.g. tachycardia, tachypnea, edema and puffy eyelids.

If the child fails to improve after the first hour of parenteral fluids, she/he should be assumed to have septic shock and treated with maintenance IV fluids (4 ml/kg/hr) along with fresh whole blood transfusion at 10 ml/kg *slowly* over 3 hours.

Dehydration can be prevented in a SAM child with watery diarrhea by feeding F-75 feeds (step 7) and replacing the stool losses with 50–100 ml of ReSoMal/half-ORS after each watery stool. Breastfeeding should be encouraged in breastfed children.

Step IV. Correct electrolyte imbalance: Dyselectrolytemia is common in malnutrition due to poor intake, losses in diarrhea/vomiting and redistribution of body fluids, even in absence of clinical signs.

All malnourished children have *excess body sodium* due to renal retention, despite low or normal plasma sodium levels and should receive low-salt diet. Hypertonic fluids should be strictly avoided.

Hypokalemia is common due to redistribution of body fluids, which may be asymptomatic or presents with muscular weakness and abdominal distension. Asymptomatic hypokalemia can be treated with oral potassium supplements 3–4 mEq/kg/day for 2 weeks as commercial potassium chloride solution (20 mEq/15 ml),given mixed with feeds. In cases on IV fluids, potassium must be added to IV fluids as 2–3 mEq/kg/day, after the child has passed urine.

Hypomagnesemia is common due to reduced muscle mass and may be corrected by oral magnesium supplementation as 0.8–1.2 mEq/kg. On day one, all malnourished children must receive single dose of IM magnesium sulfate (0.3 ml/kg, max 2 ml).

Hypocalcemia may be present due to low albumin-bound fraction, but rarely needs to be treated as ionic calcium is usually normal.

Step V. Treat and prevent infections: Infections are common but may be difficult to recognize due to poor inflammatory response and absence of constitutional signs, e.g. fever. All cases of SAM on admission must be presumed to have infection and treated with empirical antibiotics. Presence of hypothermia, hypoglycemia, shock and bleeding tendencies indicates potentially serious underlying infection.

Choice of empirical antibiotics and duration of therapy varies with severity of sepsis and presence of complications **(Table 6.8)**, which should be modified after culture reports. Some workers also suggest metronidazole (PO 30 mg/kg/d q8h 7 days) to cover anaerobic infections. Antimalarial therapy is indicated only if smear is positive.

TABLE 6.8: Antibiotic therapy in SAM

No complications:
PO Amoxicillin 60 mg/kg/d q8h × 5 days
Complications: (excluding shock, meningitis or dysentery)
IV Ampicillin 200 mg/kg/d q6h × 7 days ***with***
IV Gentamycin 7.5 mg/kg/d q24h × 7 days
Add:
IV Cloxacillin 100 mg/kg/d q6h
(In suspected staphylococcal infections)
Septic shock or no improvement in initial hours:
IV Cefotaxime 150 mg/kg/d q8h ***or***
IV Ceftriaxone 100 mg/kg/d q12hr ***with***
IV Gentamycin 7.5 mg/kg/d q24h
(No second dose of gentamycin, till urine is passed)
Meningitis: (14–21 days)
IV Cefotaxime 200 mg/kg/d q6h ***or***
IV Ceftriaxone 100 mg/kg/d q12h ***with***
IV Amikacin 15 mg/kg/d q8h
Dysentery:
IV/PO Ciprofloxacin 30 mg/kg/d q12h × 3 days ***or***
IV Ceftriaxone 100 mg/kg/d q12-24h × 5 days

Step VI. Correct micronutrient deficiencies, *which* are common but often asymptomatic due to adaptive mechanisms.

Vitamin A supplementation is indicated in age dependent single oral dose (2, 00,000 IU <1 yr, 1, 00,000 IV in 0.5–1 yr and 50,000 IU <6 mo) on admission. However, in cases with clinical signs of deficiency, three doses on day 1, 2, 14 are required. Intramuscular administration is needed (half of the oral dose) in cases with severe anorexia, edematous malnutrition or septic shock. WHO recommends daily vitamin A supplements (5000 IU/day) and not the single dose therapy as above, except when feeds not fortified with vitamin A.

Vitamin K (IM 2.5 mg) is also recommended as singledose on the day of admission.

Other vitamin-mineral supplements, except iron, must be given from the day of admission for at least 2 weeks **(Table 6.9)**, either separately or as combined preparation. Multivitamin preparation should also contain vitamin A, C, D, E and B_{12} along with other minerals, in doses twice of the recommended dietary allowance.

Iron supplements should be delayed till the baby starts gaining weight and is on catch-up diet for at least 2 days, as it may be utilized by organisms for their metabolism and deteriorate the underlying infection. It should be continued for at least 2 months to replenish stores. Transfusion should be avoided due to potential risk of CCF, indicated only in cases with hemoglobin <4 gm or

TABLE 6.9: Micronutrient supplements in SAM

On day 1
• PO/IM Vitamin A: Single age-dependent dose*
• IM Vitamin K 2.5 mg single dose
From day 1–14 (all orally)
• PO Multi-vitamins (in twice RDA dose)**
• PO Folic acid 1 mg/d (5 mg on day 1)
• PO Zinc 2 mg/kg/d
• PO Copper 0.3 mg/kg/d
From the time weight gain starts
• PO Iron 3 mg/kg/d q12h

*see Table 6.14
**see Table 5.1

TABLE 6.10: Recipe for starter (F-75) diet

Contents (per 1000 ml)	*Milk-based*	*Cereal-based**
Cow milk (ml)	300	300
Sugar (gm)	100	70
Powdered puff rice (gm)	—	35
Vegetable oil (gm)	20	20
Water make up to (ml)	1000	1000
Energy (kcal/100 ml)	75	75
Proteins (gm/110 ml)	0.9	1.1
Lactose (gm/100 ml)	1.2	1.2

*Cook for 4 minutes

TABLE 6.11: Recipe for catch-up (F-100) diet

Contents (per 1000 ml)	*Milk-based*	*Cereal-based**
Cow milk (ml)	900	750
Sugar (gm)	75	25
Powdered puff rice (gm)	—	70
Vegetable oil (gm)	20	20
Water make up to (ml)	1000	1000
Energy (kcal/100 ml)	100	100
Proteins (gm/110 ml)	2.9	2.9
Lactose (gm/100 ml)	3.8	3.0

*Cook for 4 minutes

4–6 gm with respiratory distress. In them, whole blood may be transfused (10 ml/kg over 3 hour), along with IV furosemide (1 mg/kg) at the beginning of transfusion. Packed cells transfusion (5–7 ml/kg) should be used instead of whole blood in presence of CCF. All cases should be monitored or fluid overload. Blood transfusion should not repeated in next 4 days, if avoidable.

Step VII. Initiate re-feeding: Feeding should begin as soon as possible, though cautiously due to fragile physiological state and limited homeostatic capacity. Early feeding at this stage aims to provide sufficient energy and proteins for basic metabolic processes, without expectation of weight gain. However, these children have poor appetite and limited capacity to handle proteins, fats and solutes. Important considerations to initiate re-feeding are as follows:

- Recommended dietary intake during this phase is~*100 kcal/kg/d of energy, 1–1.5 gm/kg/d of proteins and 130 ml/kg/d of fluids of actual weight* (100 ml/kg/d fluid, if the child has severe oedema).
- Starter feeds must provide ~ 75 kcal and ~ 0.9 gm protein per 100 ml **(F-75),** which may milk-based or cereal-based, preparedly locally **(Table 6.10)**.
- Frequency and volume of feeds depend on the acceptance. Usually, small and frequent (8–12/day) feeds are required in the beginning, given throughout the day, including in night. Volume of each feed may be increased gradually as the appetite improves.
- Oral feeds are preferable, though nasogastric feeding is indicated if the baby is unable to consume at least 80% of offered feeds.
- Breastfeeding should be encouraged *ad libitum* in breastfed cases, along with starter feeds.
- All cases should be monitored daily for body weight, losses in stools/vomiting and 24-hr intake, carefully assessing the feeds offered and leftovers.

Step VIII. Feeding for Catch-up growth: Once the appetite returns and child is stabilized, usually after a week, rehabilitation phase begins to rebuild wasted tissues and ensure weight gain. Important considerations for catch-up diet during this phase are as follows:

- Catch-up diet **(F-100)** must be relatively more energy-dense, containing ~100 kcal and 2.9 gm protein per 100 ml, which may milk-based or cereal-based, preparedly locally **(Table 6.11)**.
- To being with, starter-formula feeds (F-75) must be replaced with the same amount of catch-up formula (F-100) for first two days, followed by gradually increasing the each feed by 10 ml, until some feed remains uneaten. Usual intake at this stage is expected to be ~30 ml/kg/feed or ~200 ml/kg/day.
- To begin with, child should receive at least 8 feeds/day of catch-up formula. Gradually, some of these feeds may be replaced by ready-to-use therapeutic foods (RUTF, discussed later) or locally prepared therapeutic foods or modified family foods with comparable energy and protein concentration, e.g. *khichri or halwa*, to prepare the child for discharge on home diet. Breastfeeding should be continued *ad libitum*, in breastfed children.
- Child should be encouraged to eat as much as possible and offered more feeds next time, if finished everything. Frequency may be reduced gradually to 6 feeds/day, as the volume per feed improves. *At the end of this phase, target is to give 200 calories ml/kg/day and 4–6 gm/kg/day of proteins, of actual weight.*

- All cases should be monitored for daily weight gain, expected to be ~10 gm/kg/day. Child should be reassessed for underlying infection or psychosocial problems, if weight gain is inadequate. All cases should also be monitored for signs of heart failure.
- Infants <6 months should not given undiluted F-100 due to risk of solute overload and must be managed with breastfeeding and/or F-75.

Failure to respond during rehabilitation phase is defined as *weight gain <5 gm/kg/day*, while those with gain between 5 and 10 gm/kg/day are considered to have moderate response. Poor weight gain may be due to: (a) inadequate feeding, (b) specific nutrient deficiencies, (c) underlying infection or systemic disease, and (d) emotional deprivation.

Failure to respond is further classified as *primary failure* when child fails to: (a) regain appetite by 4th day, (b) start loosing edema by 4th days, (c) loose edema by 10th day, and (d) gain weight by at least 5 gm/kg by 10th day. *Secondary failure* denotes weight gain of <5 gm/kg/day for three consecutive days in rehabilitation phase.

Step IX. Provide sensory stimulation and emotional support: Developmental delay and behavioral changes are common in SAM children. Emotional and physical stimulation is an integral part of management in these cases and includes: (a) tender and loving care, (b) cheerful and stimulating environment, (c) encouragement of physical activity, (d) maternal involvement in child care, and (e) structured play-sessions including language and motor activities with the help of toys, etc.

Step X. Prepare for follow-up after recovery: Most cases need ~10–15 days of hospitalization, while remaining part of rehabilitation phase may be completed at home, followed by periodic follow-up for 4–6 month to prevent recurrence. While preparing for the discharge:

- Child should be gradually switch-over from catch-up diet to regular family meals, in adequate quantity and appropriate quality.
- Mother must be trained to follow correct feeding practices, including need for breastfeeding, preparation of nutritious feeds and feeding frequently.
- Immunization must be completed for age.
- De-worming must be done with single oral dose of Albendazole 200 mg (400 mg for >2 yr).
- Follow-up plan must be shared with mother, who should also be trained to recognize signs which need immediate medical attention.

Criteria for discharge: WHO recommends that SAM cases should be discharged only after achieving: (a) Wt for Ht >-2 SDS/z-score, (b) no edema for at least 2 weeks, and (c) MUAC > 12.5 cm. WHO does not recommend use of *percentage weight gain* as criteria for discharge. However, considering the patient-load, Government of India guidelines recommend that a SAM case can be discharged from the hospital if:

- has gained >15% of pre-admission weight with satisfactory gain for 3 consecutive days (>5 gm/kg/day),
- accepting adequately the nutritious foods that the mother can prepare at home,
- all infections and other medical complications have been treated,
- has been provided with micronutrients,
- has been fully immunized, and
- mother has been trained for good feeding practices and sensory stimulation at home. She must also be able recognize the signs which need immediate medical assistance.

On discharge, these cases should be transferred to the outpatient therapeutic program (OTP), discussed later, and must be followed up every 2 weeks in first month and then monthly thereafter until weight for height reaches >-1 Z/SD-score.

Re-feeding (Recovery) syndromes: While rarely seen at present due to the use of standard guideline-based management, children recovering from SAM are prone to develop many complications due to unmasking of subclinical nutrient deficiencies and should be carefully monitored for:

- *Diarrhea* due to relative lactase deficiency and other malabsorption states, precipitated by increased nutritional intake,
- *Congestive cardiac failure* due to shift of edema fluid in intravascular compartment, following high solute and protein diet,
- *Un-masking of sub-clinical vitamin and mineral deficiencies*, e.g. scurvy, zinc deficiency, due to disturbed adaptation.

Two well-defined clinical syndromes seen during the recovery phase are *Kahn and Gomez recovery syndromes*, probably caused by unmasking of subclinical nutrient deficiencies.

- ***Kahn's recovery syndrome*** is characterized by sudden onset of tremors and encephalopathy, probably due to unmasked deficiency of gamma aminobutyric acid (GABA)–a major neuroinhibitors.
- ***Gomez recovery syndrome*** is characterized by progressive abdominal distension, ascites, hepatomegaly and diarrhea, due to secondary malabsorption and dyselectrolytemia, e.g. hypokalemia.

B. Community-based Care

Generally, SAM is managed in hospitalization set-up while MAM is managed on outpatient basis. However, it is neither possible nor desirable to provide facility-based care to all SAM children in resource-limited settings. Community-based care or home-based care is a more feasible concept for the management of malnutrition in resource-limited settings and includes:

- ***Outpatient therapeutic program*** (OTP) for children with SAM but good appetite and no medical complications or those who have been prematurely discharged from the facility-based care.

  OTP should aim to provide ~150 calories and 4 gm/proteins per day till complete recovery, using frequent energy/protein dense meals either as read to use therapeutic food (RUTF) or home-based modified diet along with micronutrient supplementation. Children are followed-up weekly at an OTP site in a community setting, for periodic check-ups and replenishment of RUTF.
- ***Supplementary feeding program*** (SFP) for children with MAM or those who have been graduated from OTP. SFP provides for dry take-home rations and routine basic treatment.

However, *facility-based care is a must for* children with SAM and poor appetite (failed appetite test) or associated medical complications.

Ready-to-use therapeutic food (RUTF) is an energy-dense mineral/vitamin-enriched food, specifically designed to treat SAM cases under OTP care. Although similar to F-100 in formulation, RUTFs have been shown to promote faster rate of recovery.

An ideal RUTF should be: (a) caloric dense with adequate proteins, vitamins and minerals, (b) palatable and acceptable, (c) affordable cost, (d) stable with long-shelf life, and (e) easy to administer, and (f) available in suitable packs to avoid wastage.

RUTF is an oil-based preparation that contains a little water to make it microbiologically safe for storage. Since it is eaten uncooked, RUTF is also time-saving with no loss of micronutrients during cooking.

While commercial RUTFs are available in some countries, low-cost RUTF can be prepared locally using simple and easily available ingredients, e.g. whole milk powder (30 gm), peanut butter (25 gm), sugar (28 gm) and vegetable oil (15 gm), fortified with micronutrients. Each 100 gm of this RUTF provides 520–550 calories, including 45–60% from fats and 10–12% from proteins. It can be stored for 3–4 months without refrigeration and should be fed directly with plenty of water.

However, RUTF should not be confused with ready to-use foods (RTUF), e.g. maggi noodles, and should be used only for therapeutic purpose and not as supplementary food, for limited time period (4–8 weeks) until the child recovers from SAM.

RUTF *vs* Modified home diet: Government of India does not approve use of RUTF and favours the use of modified home diet or locally prepared therapeutic diets for these children, along with supplementary nutrition. Several locally prepared therapeutic diets have been developed and being used for community-based management of acute malnutrition programs of different states, e.g. Telangana. Some states provide for take-home ration program at community centers to provide 150–180 cal/kg and 3.5–5.5 gm/kg of proteins.

Amylase rich foods (ARF) are easily digestible and enriched sources of proteins and vitamins, prepared by *soaking* common cereals or pulses in water for 12 hours > *sprouting* by wrapping in a moist cloth for 48 hours, > *drying* > *roasting* > *grueling* to make porridge grinding, before storage. One teaspoonful (5 gm) of this powder may be added in each infant food after cooking. On soaking, the amylase breaks down grain-starch into easily-digestible maltodextrins, reducing the viscosity and bulk of diet. Germination also enhances vitamin content.

6.1.6 SEVERE ACUTE MALNUTRITION IN INFANTS < 6 MONTHS

Severe acute malnutrition infant below 6 months is less likely in children with exclusive breastfeeding, usually seen in top-fed infants and diagnosis rests on following criteria:

- Weight/height < 3 SDS or z-score, or
- Bilateral symmetrical edema or visible wasting

MUAC cannot be used for diagnosis of SAM in infants <6 months and use of wasting for diagnosis of SAM should be made with utmost caution.

Management of SAM in infants <6 months is similar to management in older children with following considerations:

- All these infants should preferably be hospitalized irrespective clinical status, unless there are overriding barriers.
- In view of the high-risk of underlying sepsis, all these infants should receive parenteral antibiotics in initial days of hospitalization or a course of oral antibiotics, e.g. Amoxicillin, if cannot be hospitalized.
- Breastfed children should continue breastfeeding with assessment of local breast/nipple problems, position, attachment and adequate intake. Mother should be encouraged for frequent breastfeeding after proper lactation counseling.
- In non-breast infants (in order of preference).
  - Attempt should be made re-initiate lactation, using supplementary sucking techniques (discussed below), or
  - Provide expressed breast milk or milk from human milk banking or
  - Use a generic infant milk formula or started F-75 diet or diluted catch-up F-100 diet (by adding 30% water), either alone or in addition to the breast milk. Undiluted catch-up diet should not be used due to high solute load.
- Assess the physical and mental status of mother, with appropriate counseling and support.

Supplementary sucking techniques (SST) aim to re-establish breast milk output in mothers who have stopped BF due to some reason before consultation and includes:

- ***Non-nutritive sucking,*** i.e. to place the baby on the breast at least 8–10 times/day for 10–15 minutes every time, even in the absence of milk output.
- ***Drip and drop method,*** in which a nasogastric tube connected to milk/formula filled cup (~100–130 ml) is fixed with an adhesive tape over the nipple and baby is encouraged to suck on nipple while milk is gradually dripped over it. Cup is kept 5–10 cm below the nipple level so the milk does not flow too quickly. Sucking efforts by the baby stimulate prolactin reflex to re-establish BM output. Gradually the cup should be lowered further to encourage stronger sucking efforts.

SST should initially be done on both breasts 4–6 times a day along with intermittent *katori*/spoon feeding and the frequency should be reduced gradually over next 7–14 days. If the baby does not finish supplementary feed after few days but is gaining weight, it means that breast milk output is increasing.

Discharge: Infant <6 months with SAM should be discharged only if weight for height has reached >–2 z-score, though early discharge may be considered in cases with: (a) continuous weight gain (> 5 gm/kg/day) for > 2 weeks, (b) good appetite (c) absence of medical complications, (d) availability of effective alternative supervision.

6.1.7 MODERATE ACUTE MALNUTRITION

AS stated earlier, moderate acute malnutrition is defined as: (a) weight for height between – 2 to – 3 z-score, (b) MUAC between 11.5–12.4 cm, and (c) absence of edema or visible wasting.

Children with MAM are best managed at home, unless have some other co-morbidity or medical complications. Some cases can be managed in nutritional rehabilitation centers (NRCs) in early stages. Important considerations in the management of MAM include:

- Initial assessment for complications and appropriate management, including de-worming.
- Ensure minimum daily caloric intake of 150 calories/kg and 2–3 grams proteins/kg from all sources including regular and supplementary feeds.
- Supplementary foods must be energy-dense providing 1.5–2 cal/gm (instead of usual 0.8 cal/gm) along with-35–45% calories from fats with minimum 5% from n-6 PUFA, 0.5% from n-3 PUFA, linolenic acid:alpha-linoleic acid ratio of 5–15% and protein digestibility corrected amino acid score (PDCAAS) of >70% (*WHO 2014 recommendations*). A cereal/legume mix diet with milk and animal protein sources may be used in appropriate quantity and frequency. Supplementary foods through various sources, e.g. RUTF or home-made items may be used for this purpose.
- Micronutrient supplementation or fortification of foods.
- Nutritional counseling for appropriate volume, frequency and diversity of home diet, cooking practices, food hygiene, etc.

6.1.8 PREVENTION OF UNDERNUTRITION

Undernutrition is more of a socio-economic problem, rather than the medical disease. A comprehensive approach is required, especially in developing countries to overcome it. Important preventive steps against PEM include:

I. Promotion of general health and nutrition:

- ***Actions at family level*** to promote:
  - Correct breastfeeding and weaning practices
  - Consumption of cheap, local, nutritive foods
  - Correct cooking practices
  - Avoidance of wrong food taboos and habits
  - Equitable food distribution in the family
  - Setting of kitchen gardens/poultry keeping
  - Correct feeding practices during illnesses
  - Nutrition in pregnant/lactating mothers
  - General child health/hygiene
  - Family planning practices
- ***Action at community level:***
  - Nutritional surveillance
  - Nutritional education
  - Development of local low-cost foods
  - General measures to improve child health, e.g.
    - Improved water supply and sanitation
    - Widespread immunization services
    - Preventive/curative healthcare facilities
  - Creation of local job opportunities
- ***Action at national level*** to promote:
  - Agricultural production
  - Food-storage facilities and public distribution
  - General rural/urban-slum development
  - Poverty-alleviation measures,
  - Food subsidies to high-risk population
  - Targeted health and nutritional programs
- ***Action at international level:***
  - International aids for socioeconomic development.
  - World Food Program (1963) to meet food requirements in needy countries.
  - International cooperation during emergencies, e.g. natural disasters and wars.

II. Specific protection to high-risk children:

- Nutritional surveillance in preschool children
- Nutritional supplementation/food fortification
- Periodic deworming and iron supplements, etc.
- Immunization to control infections

III. Early diagnosis and management:

- Growth monitoring of under-5 children
- Nutritional assessment at all contact points
- Early diagnosis and management of PEM
- Early diagnosis and treatment of infections

IV. Follow-up and rehabilitation:

- Nutritional rehabilitation centers/services
- Follow-up of recovered cases

National Nutrition Policy, (1993) to tackle problem of undernutrition, has four major components:

a. Nutritional intervention for vulnerable groups, e.g. children, pregnant mothers and adolescent girls,
b. Fortification of essential foods,
c. Popularization of low-cost nutritious food,
d. Control of micronutrient deficiencies among vulnerable groups.

Many supplementary nutrition programs are operational in India to achieve these objectives, some as follows:

Mid-day Meal Programme was first launched in 1925 for disadvantaged children in Madras Municipal Corporation. In 1995, it was converted to a centrally-sponsored scheme for children in classes I–V of the government, government-aided and local body schools. Coverage was later extended to alternative educations institutions and then to children in upper primary classes (VI–VIII) in 2004.

Objectives: Mid-day meal program aims to provide ~1/3rd of the calories and ½ of the protein requirements, using low-cost, locally available and acceptable food items, to: (a) improve the nutritional status of children, and (b) to encourage them to attend school regularly and prevent drop-outs.

Beneficiaries include all children up to 8th standard, studying in government or government-aided schools, including alternative education centers, e.g. madarsa.

Activities: Under this scheme, only cooked lunch with minimum 300 calories and 8–12 grams of protein is provided to primary school children (classes I–V); and 700 calories and 20 grams of protein to those in higher classes. Mid-day meal should be considered only as a *supplement* and not the replacement of regular meals.

Organization: Central government provides free food grains @ 100 grams per child per school day, along with transport and cooking costs. However, the program is carried out by local authorities. Non-government organizations or self-help groups are used for cooking, under supervision of local committees or parent-teacher associations.

Integrated child development scheme (ICDS) provides supplementary nutrition is to children <6 years and pregnant mothers, along with other services for children 6 months –6 years, it provides 500 cal and 12–15 gm proteins/day (800 cal and 20–25 gm proteins/day to children with SAM) (for details See Ch 28.4).

Poshan Abhiyaan (***P**rime Minister's **O**verarching **S**cheme for **H**olistic **N**utrition*), previously termed as *National Nutrition Mission*, was launched in 2018 to:

- To reduce prevalence of undernutrition, stunting, anemia and low birth weight by 2% annually,
- To enhance nutritional status of children, adolescents, pregnant women and lactating mothers.

Implemented by *Ministry of Women and Child Development* under policy directions from *National Council for Nutrition*, Poshan Abhiyaan involves:

- Mapping of various schemes related to malnutrition and develop a robust convergence between them,
- Real-time monitoring of data and encouraging Anganwadi workers to use IT-based tools for this purpose,
- Measurement of height of children at Anganwadi centers,
- Scaling up of the interventions under World Bank assisted ICDS.
- Setting-up Nutrition Resource Centres, social audits and involving masses for participation in nutritional activities.

6.2 VITAMIN A DEFICIENCY

Vitamin A deficiency, till recently, was the commonest cause of preventable blindness in Indian children. While the prevalence of severe disease has substantially declined in recent years due to preventive programs, subclinical deficiency continues to be common with a prevalence of ~1–3% in preschool children.

Physiology: Vitamin A is a fat-soluble vitamin **(Table 6.12)**, existing in two forms:

a. *Pre-formed vitamin*, e.g. *retinol,* present in animal sources; and
b. *Pro-vitamin*, e.g. β-*carotene*, present in plant sources, which is converted to retinol in the gut.

Retinol is actively accumulated in liver (as retinyl palmitate) during last trimester of pregnancy and breastfeeding. Postnatally, retinol is better absorbed than β-carotene and transported in blood, bound to a retinol-binding protein.

RDA for vitamin A in children is ~350–600 µg/day increasing with age to ~800–1000 µg/day in adolescents, all values in terms of retinal equivalent (1 RE = 3.3 IU)

Dietary sources: Important source of vitamin A include yellow fruits, milk and animal products and fortified foods and at least half of the RDA should be derived from animal sources.

TABLE 6.12: Vitamin A at a glance

RDA: 350–1000 µg RE (1200–3000 IU)
Dietary sources
• ***Plant foods:***
Yellow fruits: Mango (1000 IU), papaya (400 IU)
Vegetables: Carrot (4000 IU), spinach, amaranth
• ***Animal foods:***
Milk products: Butter, margarine, cheese
Non-veg: Eggs, liver, fish, cod liver oil (54,000 IU)
• ***Fortified foods:*** Vansapati ghee
Functions
– Production of *rhodpsin*—night-vision pigment
– Maintenance of epithelial integrity
– Anti-oxidant (free-radical scavanger)
– *Others* - in bone metabolism, spermatogenesis, etc.
Deficiency states
• Xerophthalmia
• Phyrnoderma (follicular hyperkeratosis)
• Susceptibility to infections
Toxic effects (hypervitaminosis)
• *Acute:* Pseudotumor cerebri
• *Chronic:* Dry skin, alopecia, hyperostosis (limb-pains)
• *Carotenemia:* Yellow discoloration of skin

RE: Retinol equivalents (1 µg = 3.3 IU)

Functions: Vitamin A is essential for retinal functions, maintenance of epithelial integrity to resist infections and removal of toxic free-radicals from body.

Vitamin A Deficiency (VAD)

Etiology: VAD is most common in toddlers and preschool children from low socioeconomic status. Common causes of VAD include:

a. Dietary deficiency
b. Malabsorptive states, e.g. chronic diarrhea, worm infestations, etc.
c. Impaired metabolism, e.g. in chronic liver disease
d. Reduced transport proteins, e.g. in malnutrition, nephrotic syndrome, etc.
e. Higher requirements in infections, e.g. measles.
f. Less intrauterine stores, e.g. in preterms
g. *Darrier disease*—a genetic defect (*vitamin Adependency*).

Clinical manifestations of VAD may be divided into two broad groups—ophthalmic (xerophthalmia) and extra-ophthalmic manifestations.

A. Xerophthalmia denotes a spectrum of ocular signs in VAD **(Table 6.13)** including:

- *Night blindness*, i.e. inability to see clearly in dim-light or slower dark-adaptation.
- *Conjunktival xerosis*, i.e. dry, wrinkled, lusterless, muddy conjunktiva due to cornified epithelium and *Bitot' spots*—chalky gray triangular plaques, generally near the temporal limbus, due to heaped-up dry epithelium **(Fig. 6.7A)**.
- *Corneal lesions* of variable severity: (i) *xerosis*, i.e. dull, dry and cloudy cornea, (ii) *ulcers*, limited to a few layers of cornea, or (iii) *keratomalacia*, i.e. liquefaction and rupture of full-depth cornea, leading to loss of vision **(Fig. 6.7B)**. Even mild cases may lead to corneal scarring on recovery.
- *Fundal changes*, e.g. retinal xerosis and detachment.

TABLE 6.13: WHO classification of xerophthalmia

Primary signs	*Secondary signs*
X_{1A}: Conjunctival xerosis	X_N: Night blindness
X_{1B}: Bitot's spot	X_S: Corneal scarring
X_2: Corneal xerosis	X_F: Fundal changes
X_{3A}: Corneal ulceration	
X_{3B}: Keratomalacia	

Fig. 6.7: (A) Bitot's spot; (B) Keratomalacia.

B. Extra-ocular manifestations include:

- *Phrynoderma (follicular hyperkeratosis),* presenting as dry and scaly skin with *toad-like* texture, specially over extensor aspects of extremities, e.g. dorsum of tibia, knees and elbows. Phrynoderma is also associated with essential fatty acid deficiency.
- Recurrent respiratory infections, due to squamous metaplasia of respiratory mucosa.
- Recurrent urinary tract infections, pancreatitis or parotitis due to epithelial metaplasia of urinary or exocrine tracts.
- Rarely, atrophy of genital epithelium may lead to reproductive dysfunction in adults.

Diagnosis of VAD is largely clinical, though subclinical deficiency may be identified by:

a. *Conjunctival impression cytology* (CIC), to detect loss of mucus-secreting goblet cells and epithelial metaplasia on special staining,
b. Dark-adaptation test, and
c. Low plasma carotene levels (<20 µg/L).

Treatment: As per WHO recommendation, standard treatment of VAD includes 3 age-dependent doses of

TABLE 6.14: Treatment of vitamin A deficiency (WHO)

	< 6 months	*6–12 months*	*> 12 months*
Day 1	50,000 IU	1,00,000 IU	2,00,000 IU
Day 2	50,000 IU	1,00,000 IU	2,00,000 IU
Day 14	50,000 IU	1,00,000 IU	2,00,000 IU

concentrated, preferably fat-soluble vitamin A (1,00,000 IU/ml), given orally, on day 1, 2 and 14 **(Table 6.14)**.

In cases with malabsorption or persistent vomiting, IM therapy with water soluble vitamin A (50,000 IU/ml) may be used, given as *half of the oral dose* with same schedule. Local ophthalmic treatment of corneal lesions with antibiotics, mydriatics and eye-padding is equally important.

All cases treated for VAD should receive dietary counseling and vitamin A prophylaxis till 6–8 years of age (2,00,0000 IU every 6 month) to prevent the recurrence.

Prevention of VAD includes nutritional counseling, vitamin A supplementation, fortification of dietary feeds (*see* national program below) and prevention of precipitating illnesses, e.g. measles.

National Control Programme Against Nutritional Blindness Due to Vitamin A Deficiency

Launched in 1970, currently this program is a component of National Health Mission, aimed to decrease the incidence of VAD and consequently preventable blindness. Prevalence of night blindness in pre-school children is considered as the best indicator of VAD, classified as *severe* (>5%), *moderate* (1–5%) and *mild* (<1%).

Beneficiary: Children from 9 months to 5 years.

Components of this program include:

- ***Universal prophylaxis*** with 6-monthly administration of oral vitamin A 1,00,000 IU (<1 year) and 2,00,000 IU in older children, from 6 months to 5 years of age. This protocol was first developed by National Institute of Nutrition, Hyderabad and later adopted by WHO as global strategy. Presently, first two doses are given during immunization visit at 9 months (with MR vaccine) and 15–18 months (with first booster dose). Subsequent doses at 24, 30, 36, 42, 48, 54 and 60 months of age are given in some states. IAP recommends this vitamin A administration to all children only till 3 years of age.
- ***Additional doses*** of vitamin A, after illnesses, e.g. measles, severe PEM, chronic diarrhea and long febrile illnesses.
- ***Dietary counseling,*** to encourage consumption of cheap and locally available vitamin A rich foods.
- ***Prevention of precipitating illnesses,*** e.g. measles by vaccination coverage and breastfeeding promotion.
- ***Periodic monitoring*** and evaluation.

Note: In national program, oral vitamin A is supplied as multi-dose liquid preparation (1 lac IU/ml), with a special 2 ml spoon. Only this spoon should be used and *not* the regular 5 ml spoon to avoid over-dosage.

Hypervitaminosis A

Being fat-soluble, excess vitamin A is not readily excreted in urine and accumulates in tissues with following presentations:

- **Acute hypervitaminosis**, due to acute preventive or therapeutic overdose (>3,00,000 IU), presents as *pseudotumor cerebri*, i.e. transient, self-limiting, benign intracranial hypertension with headache, vomiting, drowsiness, bulging fontanels and/or papilledema (Ch 18.4). Exact mechanism is unknown, probably relates to massive rupture of lysosomal membranes.
- **Chronic hypervitaminosis** due to prolonged vitamin A therapy, e.g. for acne, presents with anorexia, weight loss, dry pruritic skin, alopecia, tender extremities (hyperostosis on X-ray), hepatosplenomegaly and pseudotumor cerebri.
- **Hypercarotenemia,** asymptomatic, transient yellowish discoloration of skin/body fluids, due to excess consumption of β-carotene containing fruits.

Massive vitamin A administration in first trimester may also have severe teratogenic effects on fetus.

6.3 VITAMIN B COMPLEX DISORDERS

Vitamin B complex is a heterogeneous but closely linked group of water-soluble vitamins, all being important constituents of various enzyme systems. As many vitamins of this group share common source and inter-related metabolism, multiple vitamin B complex deficiencies are more common than isolated disorders.

Table 6.15 presents a synopsis of important functions, dietary requirements, sources and deficiency states for different members of this group, though the exact role of some of them is not yet well established.

Thiamine (B1) deficiency is an essential coenzyme for acetylcholine synthesis and oxidative utilization of glucose in *Krebs* cycle, also involves in synthesis of nucleic acids and fatty acids.

Thiamine deficiency in India is predominantly seen among rice-eating population of *costal Andhra Pradesh,* though the incidence has substantially markedly declined in recent years.

Etiology: RDA for thiamine is 0.2–2.2 mg/day. Although widely distributed in dietary sources, thiamine is a water-soluble and heat-labile vitamin, mainly present in outer-coating of grains. Consequently, its deficiency is endemic areas is predominantly associated with: (a) use of milled and polished rice as staple cereal, and (b) vigorous washing and prolonged boiling with excessive water during cooking.

TABLE 6.15: Vitamin B complex at a glance

Vitamins (RDA)	*Sources*	*Functions*	*Deficiency states*	*Causes of deficiency*
Thiamine (B_1) *(0.2–2.2 mg)*	Whole grain cereals Milk Non-veg foods	CHO metabolism Acetylcholine synthesis	• Beriberi • Wernicke's encephalopathy • ***Dependency states –*** Leigh disease, B, responsive anemia, Maple syrup urine disease (MSUD)	BF by B_1 deficient mothers Wrong cooking/ processing Malabsorption states Increased requirements
Riboflavin (B_2) *(0.4–3.1 mg)*	Milk and eggs Cereals, pulses, meat, *Fish are poor sources*	Cellular oxidation B_6 & folate metabolism Light adaptation?	• *Oral*: Stomatitis, cheilosis, glossitis • *Ocular*: Keratitis, photophobia • ***Dependency states –*** Pyruvate kinase deficiency	Dietary Malabsorption states Chronic diarrhea *Drugs:* Phenothiazines
Pyridoxine (B_6) *(0.1–3.0 mg/day)*	Widely distributed	CHO, P, Fat metabolism Normal CNS function	• Peripheral neuritis & Seizures • ***Dependency states –*** B_6 responsive anemia/seizures,	Dietary deficiency rare, *Drugs:* INH, Penicillamine Malabsorption states
Niacin (PP factor) *(2–22 mg)*	Direct: Non-veg diet Tryptophan rich foods: Milk and eggs	DNA synthesis	• Pellagra • ***Dependency states –*** Hartnup disease, Schizophrenia ?	Dietary (maize/jowar eaters)
Pentothenic acid *(10 mg)*	Widely distributed	Steroid synthesis	Not well established • Burning feet syndrome • Asthenia, depression, • Hyperemesis	? Dietary (rare) TPN Total parenteral nutrition
Folic acid Or folates *(25–340 µg)*	Widely distributed Deficient in goat milk Destroyed by Over-cooking	Nucleic acid synthesis Hb synthesis	• Megaloblastic anemia • Diarrhea, glossitis, cheliosis • Neural tube defects* • ***Dependency states –*** Folate metabolism defects	Dietary (rare) Increased requirements *Drugs*: Folate-antagonists e.g. methotrexate
Cynacobolamin (B_{12}) *(1.2–2.5)*	Non-veg foods Endogenous synthesis	Nucleic acid synthesis Myelination	• Megaloblastic anemia • Demyelinating diseases • Infertility • ***Dependency states –*** Methyl malonic acidemia	Dietary deficiency (rare) Intrinsic factor deficiency Malabsorptive states Increased requirements
Biotin *(Not established)*	Widely distributed	Not well-established	*Skin:* Dermatitis, alopecia *CNS:* Hypotonia, parasthesia ***Dependency state –*** Rett syndrome	Rare except— eating of raw egg white Formula feeding, Total Parenteral nutrition
Choline *(Not established)*	Widely distributed	Not well-established	? ↓ immunity, Liver/Renal injury ? therapeutically used in chorea, amnesia, ataxia	Experimental information only
Carnitine **(NE)** *(Not established)*	Widely distributed	Not well-established	?Myopathy, organic aciduria	Not known, hereditary

RDA: Recommended dietary allowance; **BF:** Breastfeeding; **TPN:** Total parenteral nutrition; **CHO:** Carbohydrate; **P:** Protein

Other causes include: (a) breastfeeding by thiamine-deficient mothers, and (b) total parenteral nutrition.

Clinical spectrum of thiamine deficiency is extremely wide, ranging from non-specific manifestations to well-defined syndromes, e.g. *beriberi* and *Wernicke's encephalopathy.*

- ***Beriberi***, may be classified as: (i) dry beriberi, (ii) wet or cardiac beriberi, and (iii) infantile beriberi. These cases present with:
  - *General features*, e.g. mental changes (irritability, apathy) failure to thrive and gastrointestinal upsets like anorexia, nausea and vomiting.
  - *Dry beriberi* with predominant neurological manifestations, e.g. peripheral neuritis (paresthesia, hyporeflexia, calf pains), ocular signs (ptosis/optic atrophy) and hoarseness/aphonia due to laryngeal nerve paralysis (characteristic).

  - *Wet or cardiac beriberi* with predominant cardiac manifestations, e.g. CCF with edema, cardiomegaly and pericardial effusion.
  - *Infantile beriberi* presents at 2–4 months of age with vomiting, peripheral neuropathy and puffiness, in breastfed infants of thiamine-deficient mothers.
- ***Wernicke's encephalopathy*** is a rare manifestation of thiamine deficiency in severe undernutrition or unsupplemented parenteral nutrition, presenting with irritability, ataxia, ophthalmoplegia and altered sensorium.
- ***Non-specific manifestations*** are more common in endemic as well as non-endemic regions than well-defined beriberi, presenting with anorexia, mild calf tenderness and absence of ankle/knee jerk.

Diagnosis is best established by clinical response to thiamine administration, though biochemical tests, e.g. *low RBC transketolase levels* or *elevated urinary glyoxalate excretion* indicate subclinical deficiency.

Management includes oral or parenteral thiamine administration (5–10 mg/day) for at least 6 week, followed by low-dose oral supplements (0.5–1.5 mg/day) and proper diet. Mothers of infantile beriberi, even if asymptomatic, should be treated with oral thiamine (50 mg/day).

Riboflavin (B_2) deficiency is a cofactor for various enzymes involved in cellular oxidation, energy metabolism and erythropoiesis. Riboflavin deficiency is rarely isolated, usually a part of multivitamin deficiency in sick children.

Etiology: RDA for Riboflavin is 0.5–3.0 mg/day. Deficient dietary intake or malabsorptive disorders, e.g. chronic diarrhea are most important causes of riboflavin deficiency, though sub-clinical deficiency may occur in newborns on phototherapy (destroys riboflavin) or during drug therapy, e.g. phenothiazines (interfere with its metabolism).

Clinically these cases present with:

- *Oral signs:* For example, angular stomatitis, cheilosis, glossitis
- *Ocular signs:* For example, keratitis, conjunktivitis.
- *Others:* For example, neuromotor dysfunction, poor wound healing or normocytic normochromic anemia.

Diagnosis is clinical, though subclinical deficiency may be detected by decreased urinary riboflavin excretion (<30 mg/day) or low *glutathione reductase* content in RBCs.

Treatment includes PO riboflavin (3–10 mg/day) till disappearance of signs, followed by adequate dietary intake and treatment of primary cause. Severe or non-responsive cases may need intramuscular riboflavin (2 mg TDS) in early stages.

Niacin (B_3) deficiency (Pellagra) is a component of two important glycolytic enzymes—nicotinamide adenine dinucleotide (NAD) and NAD phosphate, as well as a regulator of DNA synthesis and repair. Nutritionally, it is available as:

- *Preformed niacin* or nicotinic acid, mainly in non-vegetarian foods, e.g. meat and fish; or
- Synthesized from its precursor—*tryptophan,* mainly present in milk and eggs (60 mg tryptophan yields ~ 1 mg of niacin).

Cereals and vegetarian diet are poor sources of free niacin as well as tryptophan.

Etiology: RDA for niacin is 2–22 mg/day. Niacin deficiency is prevalent in *maize-eating* populations, dueto high leucine content in maize that interferes with endogenous conversion of typtophan into niacin (aminoacid imbalance). However in India, it is mainly seen in *jowar-eating* population of Telangana, due to same reason.

Clinically, *Pellagra, the* prototype manifestation of niacin deficiency, presents with a triad of *3 D's*, as follows:

- ***D**ermatitis*, i.e. photosensitive rashes on exposed parts of body, often described as *pellagrous glove* (hands), *boot* (legs), *necklace* (neck), etc. Chronic cases may develop vesicobullous, weeping, desquamating or hyperpigmented lesions.
- *Chronic **D**iarrhea* with/without vomiting.
- ***D**ementia* with depression, dizziness, disorientation, delirium and burning sensation/numbness (paresthesia).

Diagnosis rests on clinical triad, dietary history and response to niacin therapy. Reduced urinary excretion of *N-methyl nicotinamide* (a metabolite) has been used as an indicator of subclinical deficiency.

Treatment includes oral niacin supplementation (50–300 mg/day). IV niacin (100 mg) may be given in severe cases, though it lead to an unpleasant sensation of local heat and flushing, and rarely the cholestatic jaundice. Avoidance of sun-exposure, soothing topical agents over skin lesions and treatment of co-existing vitamin deficiencies is also necessary.

Vitamin (B_6) deficiency includes three compounds—pyridoxal, pyridoxine and pyridoxamine, each convertible to *pyridoxal phosphate*—a co-factor for many neuroenzymes, e.g. GABA, apart from other functions. Consequently, seizures and peripheral neuropathies are most common manifestations of pyridoxine deficiency.

Etiology: RDA for pyridoxine is 0.1–3.0 mg/day. Pyridoxine deficiency is rarely dietary, due to adequate vitamin content in milk and cereals. It is mainly caused by: (a) chronic diarrhea and malabsorptive states, (b) treatment with pyridoxine-antagonists, e.g. INH, penicillamine, etc. and (c) dependency states, due to

genetically abnormal structure/function of vitamin B_6 dependent enzymes.

Important *dependency states* include pyridoxine-dependent seizures, anemia and homocystinuria.

Clinically, these cases present with one or more of following four features: (a) peripheral neuritis, (b) seizures, (c) microcytic hypochromic anemia, and (d) dermatitis with cheilosis, glossitis and seborrhea around eyes, nose and mouth.

Pyridoxine-related seizures include:

- ***Deficiency seizures*** due to dietary deficiency in formula-fed children. These seizures are typically generalized and present in infancy, beyond neonatal period.
- ***Dependency seizures*** due to: (i) genetic defects in pyridoxine-dependent enzymes, or (ii) mega pyridoxine therapy in pregnant mothers for hyperemesis gravidarum. These seizures are typically intractable myoclonic seizures, beginning in first week of life (termed 5th day fits). A *hypsarrhythmic pattern* on EEG is diagnostic, which rapidly responds to pyridoxine administration.

Diagnosis must be suspected after exclusion of other causes for seizures and anemia. In a suspected case, 100 mg pyridoxine is given intramuscularly, preferably with concomitant EEG recording. Immediate control of seizures and EEG abnormality suggests pyridoxine deficiency/dependency.

Tryptophan loading test, a biochemical test, to differentiate between pyridoxine deficiency and dependency states, involves loading with 100 mg/kg of tryptophan that leads to increased *urinary excretion of xanthurenic acid* in deficiency states. This test is normal in dependency states.

Treatment: Pyridoxine-deficiency seizures are treated with IM pyridoxine (100 mg), followed by adequate dietary intake and treatment of primary cause. Pyridoxine-dependent seizures need long-term daily therapy (PO 10–100 mg or IM 2–5 mg).

Folic acid deficiency (pteroylglutamic acid) is essential for normal DNA synthesis and hence, folic acid deficiency mainly affects rapidly dividing cells, e.g. bone marrow (megaloblastic anemia) or in fetus (neuronal tube defects). In natural diet, folic acid exists as folates.

Etiology: Folic acid deficiency is rarely dietary due to miniscule daily requirements (25–350 µg/day), usually caused by: (a) malabsorption states, e.g. fish tapeworm infestations, (b) increased requirements, e.g. in pregnancy and hemolytic anemia, and (c) anti-folate drugs, e.g. methotrexate, pyrimethamine. *Goat and camel milk are poor sources of folic acid.*

Clinically, these cases present with four important manifestations: (a) megaloblastic anemia, (b) chronic diarrhea, (c) neurological manifestations, e.g. tremors and developmental regression, and (d) skin hyperpigmentation, specially on knuckles and thigh. Severe deficiency may also be associated with thrombotic episodes and atherosclerosis, due to altered homocysteine metabolism.

Diagnosis depends on peripheral smear (megaloblastic anemia), supported by low RBC/serum folate levels (normal: 5–20 ng/ml). *FIGLU test*, i.e. urinary excretion of formiminoglutamic acid after loading dose of histidine, may detect subclinical deficiency.

Treatment: Folic acid deficiency is treated with PO or parenteral folic acid (1–5 mg/day) for 3–4 weeks, along with concomitant vitamin B_{12} supplementation and elimination of offending drug, if applicable.

Folic acid deficiency in pregnancy is an important cause of neural tube defects in fetus, which can be easily prevented by Routine folic acid supplementation with 400 µg/day to all pregnant mothers or 5 mg/day to all mothers with previously affected child (recurrence) from 1 month before to 3 months after the conception (Ch 18.10.1).

Also *see* Chapter 19.4.2 for folic acid deficiency anemia.

Cobalamin (B_{12}) Deficiency is a cobalt-containing vitamin, essential for nucleic acid metabolism and myelin formation (*Cyanocobalamin* is the therapeutic preparation, used to treat vitamin B_{12} deficiency).

Widely present in animal sources, vitamin B_{12} is absent in plant foods, but may be endogenously synthesized by colonic bacteria. Vitamin B_{12} absorption requires hydrolysis by gastric acid and combination with a specific protein in stomach—*intrinsic factor of castle (IFc)*. This B_{12}–IFc complex attaches to specific receptor sites in terminal ileum, where B_{12} component is absorbed, transported in bound form with a plasma protein-*transcobalamin* and stored in tissues, bound to another protein-*transcobalamin I*.

Etiology: RDA for vitamin B_{12} is 1.0–2.5 µg/day. Vitamin B_{12} deficiency is rarely dietary, due to extremely low requirements, usually caused by congenital or acquired defects in its absorption, e.g. (a) congenital IFc deficiency or *juvenile pernicious anemia*, (b) malabsorption disorders, (c) *imerslund syndrome*, i.e. IFc-B_{12} receptor deficiency, and (d) congenital transcobalamin deficiency.

Clinically, vitamin B_{12} deficiency presents with a triad of: (a) megaloblastic anemia, (b) glossitis, and (c) signs of demyelination, e.g. ataxia, paresthesia, hypo/hyperreflexia (*subacute combined degeneration of cord*).

Diagnosis is usually based on:

- Megaloblastic anemia on smear that does not respond to folic acid therapy, *supported by*
- Low serum vitamin B_{12} levels (<100 pg/ml)
- Methylmalonic aciduria (>3.5 mg/day).

Schilling test is used to confirm vitamin B_{12} deficiency as well as to differentiate between IFc deficiency and malabsorption defects (Ch 19.4.2).

Treatment: Oral vitamin B_{12} therapy is unreliable due to defective absorption, though may be given as 500–1000 µg/day for 3 months, in cases without neurological signs.

Cases with neurological signs should be treated with parenteral Vitamin B_{12} (IV/IM) 250–1000 µg/day for 2 weeks, then weekly for next 2–3 months, and then monthly doses till correction of anemia. Lower range of dose (0.2 mg) may be used in infants and young children. Life-long therapy is required if cause is untreatable, e.g. juvenile pernicious anemia or malabsorption disorders.

Prevention with prophylactic Vitamin B_{12} is advised in cases with malabsorptive states.

Biotin deficiency: Role of biotin as an important co-factor of various carboxylase enzymes in carbohydrate/fat metabolism is being increasingly recognized in recent years.

Etiology: Biotin deficiency is rarely dietary, as it is also synthesized by intestinal bacteria. Important causes include: (a) excessive consumption of raw egg-white, which is rich in *Avidin*—a biotin-binding protein, (b) unsupplemented formula or parenteral feeding, and (c) genetic *biotinidase* deficiency an enzyme required to recycle biotin (*dependency state*).

Clinically, it presents with: (a) skin lesions, e.g. exfoliative dermatitis and alopecia, (b) GIT manifestations, e.g. anorexia and glossitis, and (c) neurological manifestations, e.g. extreme lassitude and muscle pains. Genetic defects may also present with *Rett syndrome*.

Diagnosis depends on dietary history, clinical features, organic aciduria and response to biotin therapy. A *filter-paper spot test* is available to screen newborns for biotinidase deficiency, testing increased excretion of 3-hydroxyisovaleric acid in urine.

Treatment includes PO or IM Biotin therapy with 2–5 mg/day for 3 weeks, though higher doses (10 mg/day) are required for dependency states.

6.4 VITAMIN C DEFICIENCY (SCURVY)

Scurvy is well-defined acute manifestation of vitamin C deficiency, though mild or subclinical deficiency states may present with impaired wound healing, bleeding gums, mild anemia and susceptibility for infections.

Physiology: Vitamin C or ascorbic acid **(Table 6.16)** is a water-soluble vitamin and hence not stored in the body and rapidly excreted in urine.

RDA of vitamin C is ~20–45 mg/day in children and 50–85 mg in adolescents, higher during infections and fever as it is not stored in body.

TABLE 6.16: Vitamin C at a glance

RDA: 20–85 mg/day
(Higher in infections *e.g.* fever, diarrhea)

Sources:
- *Richest source:* Amla (600 mg)
- *Citrus Fruits:* Guava (212 mg), orange, lemon, pineapple
- *Vegetables:* Cabbage (124 mg), tomato, green vegetables.
- *Germinated pulses*
- *Non-veg foods, e.g.* liver and kidneys (not in meat)

Functions:
- Essential for collagen formation
- Wound healing and epithelial integrity
- Facilitate iron absorption and folate metabolism
- Antioxidant effect

Deficiency states:
- *Typical:* Scurvy
- *Others:* Poor wound healing, anemia, recurrent infections

Dietary sources: Breastfeeding is an adequate source of vitamin C in early infancy. Citrus fruits, leafy vegetables and germinated seeds are rich sources of vitamin C. However, it is extremely heat-labile, rapidly inactivated on cooking and extrudes in cooking-water. Milk products and lean meat are poor sources of vitamin C.

Functions: Vitamin C essential for synthesis of: (a) normal collagen by incorporating proline and hydroxyproline, and (b) chondroitin sulphate – a component of inter-cellular matrix required for epithelial integrity and wound healing. It also facilitates, (c) iron absorption, (d) folate metabolism (conversion of folic acid into folinic acid), and (e) elimination of toxic-free radicals (antioxidant).

Vitamin C Deficiency (Scurvy)

Etiology: Scurvy is usually precipitated by sudden increase in vitamin C requirements due to infections, acute febrile illnesses, diarrhea, etc. in children with subclinical dietary deficiency, e.g. in undernutrition or top feeding. Wrong cooking practices, e.g. over-boiling of vegetables in excess water or throwing the excess cooking-water are important causes of dietary deficiency.

Clinical manifestations: Scurvy usually presents in late infancy or in toddlers, following an infective episode, e.g. diarrhea or viral infection in malnourished children. A typical case present with:

- *Skeletal signs:*
  - *Pseudoparalysis*—severe tenderness and restricted limb movements with *pithed-frog posture*
  - *Scorbutic rosary*—tender, sharp, nodular beading at costochondral junktions, due to subluxation rib epiphyses at sternal joints.
- *Skin/mucosal signs:*
  - Swollen, purple, *bleeding gums,*

- Petechial/ecchymotic perifollicular hemorrhages over skin and mucus membranes. Severe gastrointestinal or intracranial bleeds are rare.

- *Mental changes:*
  - Apprehensive facial appearance
  - Extreme irritability *or* apathy
- *Signs of subclinical deficiency:*
  - Poor wound healing
  - Moderate dimorphic anemia
  - Increased susceptibility for infections

Diagnosis of scurvy depends on:

- ***Suggestive clinical features*** with history of precipitating event, e.g. fever or diarrhea;
- ***Characteristic radiological finding***, best seen at the end of long bones at knee joint **(Fig. 6.8)** and include:
  - *Ground-glass appearance* of the shaft and epiphysis due to loss of trabecular pattern,
  - *Thinning* or *penciling of cortex* with sharply outlined epiphyseal ends,
  - *Wimberger's ring sign*-ground-glass appearance of epiphyseal centers, surrounded by a white ring of compressed collagen,
  - *White line of Frankel*—a thick, irregular, transverse, white line at epiphyseal ends due to thickened provisional zones of calcification.
  - *Trummerfeld zone of rarefaction*—a narrow zone of metaphyseal rarefaction proximal to Frankel's line, due to atrophy of subepiphyseal cortex.
  - *Angle sign*—a triangular, rarefied, lateral defect proximal to Frankel's line, representing early stage of the zone of rarefaction.
  - *Corner sign* or *Pelkan spur*—a lateral spur-like growth of *Frankel's* line, due to compression of soft shaft.
  - *Lifting or separation of periosteum* from the cortex due to sub-periosteal hematoma. Actual hematomas are visible only after 1–2 weeks of illness as *enveloping-shell appearance*, due to calcification.
- ***Biochemical diagnosis*** is required only in sub-clinical cases, based on *low ascorbic acid levels in a buffy coat* (WBCs) sample of oxalate blood (Normal: 25–40 mg/dl). A level of zero in this layer indicates scurvy, even without clinical signs. Plasma ascorbic acid levels are unreliable, though fasting levels >0.6 mg/dl exclude scurvy. Urinary excretion of >80% of dose after 3–5 hours of a loading dose of 100 mg/kg vitamin C, indicates no vitamin C deficiency.

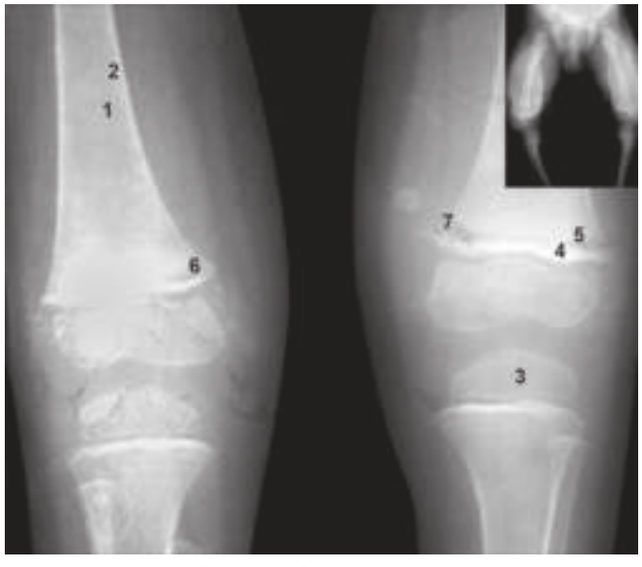


Fig. 6.8: Scurvy: X-ray

X-ray knee showing: 1. Ground glass matrix, 2. Pencil-thin cortex, 3. Ring sign, 4. Frankel's line, 5. Zone of rarefaction, 6. Angle sign, 7. Pelkan spar. ***Inset:*** Subperiosteal hematoma

D/D: Scorbutic bony lesions need to be differentiated from other cases of *pseudoparalysis*, e.g. (a) osteomyelitis/septic arthritis, (b) transient synovitis, (c) trauma, (d) congenital syphilis, and (e) leukemic bone involvement.

Scorbutic rosary is different from rachitic rosary as it is: (a) tender, and (b) has sharper margins *vs.* rounded contour of the rachitic beading.

Treatment: Vitamin C therapy (PO 200–500 mg/day for a week) is highly effective with dramatic clinical recovery within 24–48 hours, though radiological improvement may take many weeks. Recurrence must be prevented by adequate diet and therapeutic supplementation (100 mg/day) for many weeks.

Prevention includes nutritional counseling, correct cooking practices and vitamin C supplementation in lactating mothers, top-fed infants and during acute infective illnesses.

Vitamin C excess: Being a water soluble vitamin with free urinary excretion, large doses of vitamin C are well tolerated though some studies have shown higher risk of renal stones and iron load after excess vitamin C intake for long periods.

6.5 VITAMIN D DEFICIENCY (RICKETS)

Rather than a vitamin, vitamin D is now considered as a prohormone to the active form *1,25-dihydroxycholecalciferol*, which is synthesized endogenously, secreted under the control of another endocrinal product—*parathormone (PTH)* and plays a vital role in mineral metabolism.

Physiology: Vitamin D is a fat-soluble vitamin, essential for normal mineralization of growing bones **(Table 6.17)**.

RDA for vitamin D varies from 400 IU in infants and 600 IU in older children and adolescents.

Sources: *Cholecalciferol* (vitamin D_3) is the natural form of vitamin D, present as a *preformed vitamin* in animal

TABLE 6.17: Vitamin D at a glance

RDA: 400–600 IU/day
Sources:
- Endogenous synthesis under sunlight (see text)
- *Animal sources:* Animal fats and fish liver oils
- Fortified foods

Functions:
- Gut absorption of calcium and phosphorus
- Bone mineralization
- Renal reabsorption of phosphates and ? calcium

Deficiency states:
- Rickets (in children)
- Osteomalacia (in adults)

Hypervitaminosis D (develops after 1–3 months)
- *Renal:* Polyuria, polydipsia, renal failure
- *GIT:* Anorexia, vomiting
- *CNS:* Irritability, hypotonia
- *Metastatic:* Soft-tissue calcifications, osteopetrosis

sources, e.g. fats and fish liver oils. However <10% of the daily requirement is fulfilled by the diet.

Major bulk of the vitamin D is synthesized endogenously on exposure to ultraviolet rays in sunlight, from a natural pro-vitamin (*7-dehydrocholesterol*), present under the human skin. Plants do not contain vitamin D_3, though another variant (calciferol or vitamin D_2) may be derived by irradiation of a plant sterol – ergosterol.

Cholecalciferol, itself an inactive substance, needs to be sequentially hydroxylated in the liver and kidneys, to convert into either an active metabolite 1,25-dihydroxycholecalciferol ($1,25(OH)_2D_3$) or relatively inactive metabolite 24,25-dihydroxycholecalciferol ($25(OH)D_3$), depending on the needs **(Fig. 6.9)**. Active metabolite promotes calcium and phosphorus absorption from gut and kidneys as well as bone mineralization.

Functions: Vitamin D plays an important role in mineralization of bones and absorption of calcium and phosphates from gut and reabsorption from renal tubules.

6.5.1 VITAMIN D DEFICIENCY RICKETS

Vitamin D deficiency is estimated to be present in ~22–90% of infants and ~14–24% on older children and adolescents, though many cases are subclinical. Rickets is the commonest manifestation of vitamin D deficiency in children, characterized by *failure of mineralization of the growing bones*, which should not be confused with *osteomalacia*, i.e. defective mineralization of mature bones, or *osteoporosis*, i.e. demineralization of premineralized bones.

Rickets may be broadly divided into two categories: (a) Vitamin D deficiency or nutritional rickets, and (b) Vitamin D-resistant or dependent rickets **(Table 6.18)**. Nutritional rickets accounts for over 90% cases in childhood, discussed in this section.

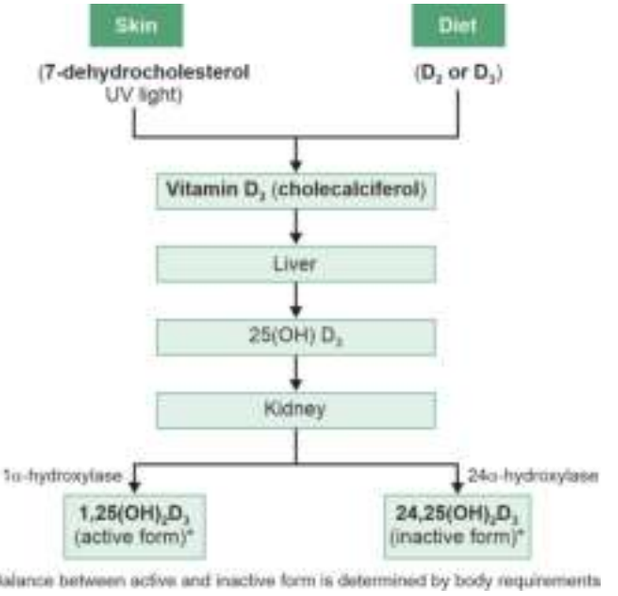


Fig. 6.9: Vitamin D metabolism.

TABLE 6.18: Etiological classification of rickets

A. Vitamin D deficiency (nutritional) rickets:
- Higher requirements in growing child
- Inadequate dietary intake
- Lack of exposure to sunlight
- Poor stores at birth—preterms, IUGR
- Malabsorption states
- Anticonvulsant therapy

B. Vitamin D resistant (refractory) rickets:
- Chronic hepatic disease
- Chronic renal disease (renal osteodystrophy)
- Hypophosphatemic rickets
  - Familial hypophosphatemia
  - Renal tubular acidosis or Fanconi syndrome

C. Vitamin D dependent rickets
- *Type 1:* Autosomal 1-hydroxylase deficiency
- *Type 2:* End-organ resistance to vitamin D

Etiologically, Vitamin D deficiency is rarely dietary, mainly seen in *rapidly-growing* children due to relatively higher requirements.

Inadequate endogenous synthesis due to limited sun-exposure in dark-skinned population, high altitudes or veil-wearing communities, e.g. muslins, is another contributory factor for rickets in India, as also poor maternal stores in vitamin D deficient mothers.

Malabsorption states, chronic liver disease and chronic renal diseases also impair vitamin D metabolism, leading to vitamin D deficiency.

Pathophysiology: Vitamin D deficiency leads to reduced calcium and phosphorus absorption from gut and reabsorption from kidneys with consequent rise in PTH levels to maintain normocalcemia. High PTH activity stimulates calcium mobilization from bones leading to:

- *Deficient mineralization* of growing osteoid tissue with typical clinico-radiological changes in rickets;
- *Increased osteoblastic activity* with elevated serum alkaline phosphate levels-*first biochemical change* in rickets.

Increased renal reabsorption of calcium leads to compensatory phosphorus excretion and low serum phosphorus levels-second biochemical change. *Normocalcemia is usually maintained in rickets by elevated PTH levels, except in severe cases*.

Clinical manifestations: Rickets commonly present at 6 months-2 years of age with bony deformities and hypotonia of supporting ligaments/muscles. Important clinical features of rickets include **(Fig. 6.10)**:

- *Craniofacial changes:*
  - *Craniotabes*—softening and thinning of skull bones with *ping-pong ball* like resilience on pressure over parietal bones, which is normal up to 3 months of age;
  - *Frontal bossing*—prominence of frontal bones;
  - *Caput quadratum*—box-head or hot cross-bun appearance due to fronto-parietal bossing;
  - Delayed closure of anterior fontanel;
  - Delayed dentition.
- *Thoracic changes:*
  - *Rachitic rosary*—round, non-tender beading due to widening of costochondral junktions;
  - *Harrison sulcus*—a groove/depression along the lower costal margins
  - Sternal deformities like *pectus excavatum*, i.e. depression of sternum, *pectus carinatum*, i.e. forward projection of sternum, or *pigeon-chest deformity;*
- *Limb deformities:*
  - Widening of wrist/ankles *(double malleolus)* due to widened epiphysis and metaphysic;
  - Gait abnormalities, e.g. knock-knee (*genu recurvatum*), bow-legs and coxa-vara;
  - Green-stick pathological fractures of long bones.
- *Spinal deformities:*
  - Kyphosis or scoliosis due to lax ligaments;
  - Short stature due to deformed spinal curvature;
- *Generalized hypotonia with:*
  - Pot-belly, due to abdominal muscle hypotonia;
  - Visceroptosis due to ligamental laxity;
  - Hyper-extensible joints (*acrobatic rickets*).
- ***Other manifestations***, e.g. excessive sweating over forehead, recurrent respiratory infections, etc.

Craniotabes

Widening of wrists

Rachitic rosary

Pectus excavatum

Knock knee

Bow legs

Fig. 6.10: Rickets: Clinical signs.

Rickets in severely malnourished children may present without clinical signs despite extensive radiological changes *(**atrophic rickets**)*.

Diagnosis of rickets depends on:

- ***Typical clinical defomities***, discussed above,
- ***Characteristic radiological changes***, best demonstrated at wrist joint **(Fig. 6.11)**, showing:
  - *Widening* of epiphyseal ends with increased space between diaphysis and epiphysis, due to poor visibility of thickened but uncalcified metaphysis.
  - *Fraying* at the visible end of long bones, (*raveled sleeve appearance)*, due to irregular mineralization of metaphysis.
  - *Cupping*, i.e. concavity at the visible end of long bones, due to poor mineralization of relatively less vascular center and pressure changes.
  - *Splaying* of the ends of long bones, due to pressure changes on poorly mineralized bones.

Other late changes include delayed bone age, costochondral widening with spatulate ribs, tri-radiate pelvis and spinal deformities.

After vitamin D administration, radiological recovery is visible in 7–10 days with appearance of *provisional zone of preparatory calcification*—a transverse

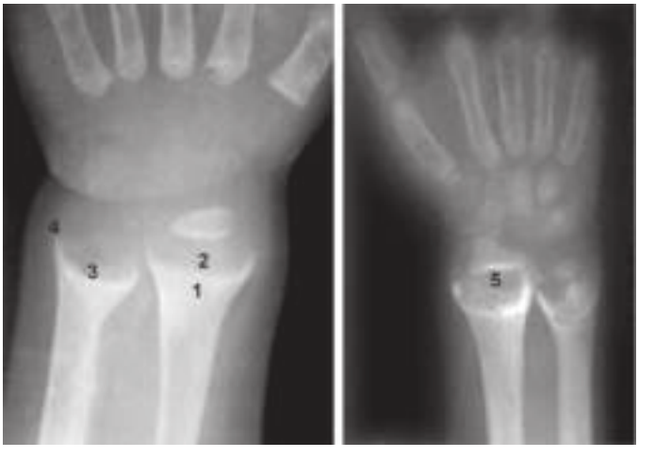


Fig. 6.11: Rickets: X-ray.

X-ray wrist showing: 1. Widening, 2. Cupping, 3. Fraying, 4. Splaying, 5. Line of preparatory calcification.

line beyond the visible end of shaft, suggestive of *healing rickets*. Absence of this zone after 3 weeks indicates possibility of refractory rickets. Complete X-ray clearance takes 2–3 months, though deformities may persist for many years.

- ***Biochemical changes*** depend on severity of disease and differentiate active disease from old deformities. Important changes in order of appearance are:
  - Elevated S. alkaline phosphatase (>20 KA units)
  - Low S. phosphorus levels (<4 mg/dl)
  - Low Ca × P index (<30)
  - Low S. calcium levels (<9–11 mg/dl)
- ***Serum vitamin D levels [25(OH)D_3]*** of < 12 ng/ml are interpreted as *deficient* while levels > 20 ng/ml are considered as *sufficient* (IAP guidelines 2021) in children to provide a buffer for periods of stress, exigency, and seasonal patterns.

D/D: Nutritional rickets need to be differentiated from vitamin D resistant/refractory rickets, discussed later. Some important indicators of non-nutritional rickets are given in **Table 6.19**.

Treatment: Conventional *Stoss regimen* was once the most widely used method to treat nutritional rickets and to differentiate them from resistant rickets. It involved administration of a single mega dose of vitamin D_3 orally or parenterally (3,00,000–6,00,000 IU) on diagnosis along with oral calcium supplements and repeating the X-ray wrist after 2–3 weeks to see for line of preparatory calcification **(Fig. 6.11)**. While appearance of this line indicates vitamin D deficiency rickets, absence of the line of preparatory calcification even after 3 weeks strongly indicates possibility of vitamin D resistant rickets and need for detailed investigations. However considering the potential risk of vitamin toxicity, stoss regimen is rarely used at present.

IAP guidelines 2021 recommend treatment of vitamin D deficiency with daily oral therapy with 2000 IU of vitamin D_3 in infants (or 3000 IU > 12 months age) for minimum 12 weeks along with daily calcium intake of 50–75 mg/kg/day (max 500 mg), followed by 400–600 IU/day as maintenance dose.

However in children with poor compliance for daily therapy, infant may be given equivalent of 2000 IU/day doses on weekly/monthly basis, while children >12 months may be given 60,000 IU every two weeks for total 5 doses (not to exceed cumulative dose of 3,00,000 IU).

Prevention of rickets as per ***IAP Guidelines 2021*** includes:

- Daily oral vitamin D supplementation (400 IU) in all infants < 1 year of age.
- No routine vitamin D supplementation is recommended beyond infancy, though adequate dietary calcium intake (500–600 mg/day; 800 mg in adolescents) and sufficient sun-exposure must be ensured. Daily sunlight exposure of 17–30 min in infants and 30–45 min in older children over 15–40% body surface area is recommended at least five times a week during noon (11AM-3PM) for preventing vitamin D deficiency across different regions and seasons.
- Routine vitamin D supplementation (400 IU/day) in children with high-risk conditions, e.g. chronic liver/renal disease, malabsorption states, chronic neuromuscular disorders and long-term therapy with anticonvulsants or steroids.
- While studies have shown lower vitamin D levels in pneumonia, tuberculosis, HIV, asthma, and ADHD/autism, causative association is not consistent and no vitamin D supplements are recommended in these cases.
- Universal maternal vitamin D supplementation is not recommended.

TABLE 6.19: Indicators of non-nutritional rickets

- Strong family history
- Rickets within first 6 months of life
- Failure to thrive, gross muscle wasting
- Signs of renal or hepatic disease
- History of mental retardation or anticonvulsant therapy
- No response to vitamin D therapy (Stoss regimen)
- *Urine:* low pH, aminoaciduria, phosphaturia

6.5.2 VITAMIN D RESISTANT RICKETS

Table 6.19 enlists some important indicators of non-nutritional rickets, the most important being no response to vitamin D therapy. Some important causes of resistant rickets are as follows:

Familial or primary hypophosphatemia, an *X-linked dominant* disease, is a leading cause of non-nutritional rickets due to defects in: (a) renal reabsorption

of phosphates, with consequent phosphaturia and hypophosphatemia, (b) conversion of 25(OH)D_3 into 1,25$(OH)_2D_3$.

Clinically, these cases usually present as toddlers with severe bow-legs and waddling gait, typically more severe in males.

Diagnosis rests on: (a) no response to vitamin D therapy, (b) similar family history, (c) heavy phosphaturia despite hypophosphatemia, and (d) absence of glucosuria, aminoaciduria and bicarbonaturia (d/d renal tubular acidosis).

Treatment includes daily phosphate supplements as *Joulie solution* (PO 0.5–1.0 gm/day q4hr), along with vitamin D_2 (2000 IU/kg/day) or preferably, 1,25 $(OH)_2D_3$ (30–60 ng/kg/day). Mega vitamin D therapy, as used in nutritional rickets, should be avoided due to the risk of hypercalcemia and nephrocalcinosis.

*(*Joulie solution: 30.4 mg phosphates/ml)*

Vitamin D-dependent rickets manifest at 3–6 months of age and are of two types:

- ***Type I***, due to 25(OH)D3–1 -hydroxylase deficiency that prevents renal conversion of vitamin D into active form, and
- ***Type II,*** due to inherited end-organ resistance.

While type I may be treated with massive doses of vitamin D_2 (2–10 lac IU/day), type II needs to be treated with 1,25$(OH)_2D_3$ (15–30 µg/kg/day).

6.5.3 HYPERVITAMINOSIS D

Hypervitaminosis D is almost always iatrogenic, due to erroneous ingestion of large doses of vitamin D during treatment of rickets. Rare cases may be related to prolonged formula feeding in preterms.

Serum vitamin D levels >100 ng/mL are considered as toxic, though levels between 50–100 ng/ml should also alert the physician to avoid further vitamin D supplementation.

Clinical manifestations develop after 1–3 months of overdose, with:

- *Hypercalcemia,* leading to:
  - Irritability, anorexia, vomiting, and constipation,
  - Cloudy cornea, retinopathy and aortic stenosis.
- *Hypercalciuria,* leading to:
  - Impaired urinary concentration with polyuria, polydipsia, dehydration and failure to thrive,
  - Nephrocalcinosis with pallor, hypertension and progressive renal failure.

Diagnosis depends on history, hypercalcemia, hypercalciuria and radiological abnormalities, e.g. generalized osteoporosis and metastatic calcifications in soft tissues. X-ray knee shows deposits of dense bone, producing the typical *spectacle sign*. ECG may suggest myocardial damage with ST elevation.

D/D includes other causes of hypercalcemia, e.g. chronic renal failure, hyperparathyroidism and idiopathic hypercalcemia (*William's syndrome*).

Treatment includes:

- Discontinue vitamin D and reduce calcium intake,
- Calcium chelators, e.g. oral $Al(OH)_3$ *or* sodium versenate for 2–3 weeks to reduce absorption,
- Cortisone 100 mg/day for 4 weeks in severe cases.

6.6 VITAMIN E DEFICIENCY

Vitamin E is a group of natural fat-soluble compounds-α-tocoferols.

Physiology: Vitamin E is an important antioxidant (free-radical scavenger), consequently considered as protective against severe inflammatory and neoplastic pathologies. It is involved in nucleic acid metabolism and stabilization of cellular membranes.

RDA of Vitamin E is ~5–10 mg of -tocoferol equivalent/day (1 mg = 1.5 IU), higher in preterms and adolescents (10–15 mg/day).

Dietary sources: Vitamin E is widely distributed in vegetable oils, fats and nuts, specially those rich in polyunsaturated fatty acids. Whole wheat, egg yolk and milk products are also rich sources of Vitamin E.

Vitamin E Deficiency

Etiology: Vitamin E deficiency is mainly seen in: (a) preterms due to poor stores, (b) chronic liver disease, (c) Malabsorption syndrome, and (d) high iron states, e.g. in hemolytic anemia.

Clinically vitamin E deficiency has been implicated in:

- Hemolytic anemia in preterms (at 6–10 weeks)
- Edema in kwashiorkor
- Degenerative neuropathy in biliary atresia or chronic liver disease, presenting as ataxia, peripheral neuropathy and posterior-column abnormalities
- Retinopathy of prematurity

Treatment: Though exact role and dose of vitamin E is not established, daily oral supplementation of 5–25 IU in high-risk children, e.g. preterms or those with chronic liver disease may prevent or reverse clinical abnormalities.

6.7 VITAMIN K DEFICIENCY

Vitamin K is a fat-soluble vitamin with very important role in hemostasis (coagulation) and to some extent, in bone metabolism.

Physiology: Vitamin K is essential for normal coagulation, via: (a) hepatic synthesis of FII, VII, IX and X, (b) activity of anticoagulant protein C and S, platelet stimulating factors, and (c) activity of osteocalcin—a calcium-binding protein.

Sources: Vitamin K available in 3 forms: natural fat-soluble vitamin K_1 in dietary sources, endogenously synthesized vitamin K_2 in gut by normal bacterial flora, and water-soluble synthetic preparations (vitamin K_3 or menadione).

Vitamin K_1 is present in animal foods, beans, green vegetables and milk, though major requirement is fulfilled by endogenous intestinal synthesis. Cow milk contains more vitamin K than human milk.

RDA of vitamin K is ~2–3 µg/day in infants, 30–60 µg/day in children and 60–120 µg/day in adolescents.

Vitamin K deficiency is seen in:

- Breastfed newborns due to low vitamin K content in breast milk.
- Altered gut flora after chronic diarrhea or prolonged antibiotic therapy, due to reduced gut synthesis.
- Defective utilization in chronic liver disease or during drug therapy, e.g. dicoumarol and aspirin.

Clinically vitamin K deficiency commonly manifests as *hemorrhagic disease of newborn* (Ch 12.17.1), though in older children, it may present as bleeding from multiple sites.

Diagnosis depends on clinical suspicion, increased prothrombin time and elevated PIVKA-II levels (***p**roteins **i**nduced in **v**itamin **K** **a**bsence*), with normal range of 17–50 mAU/ml.

Treatment: Therapeutic vitamin K preparations are available as fat-soluble vitamin K1 or aqueous synthetic analogues (menadione). Hemorrhagic manifestations may be rapidly controlled with 5 mg of any of these preparations (preferably aqueous), given parenterally. However, large doses of synthetic analogues may precipitate hemolysis in G6PD deficiency and in preterms. Blood/plasma transfusions is necessary in severe bleeding.

Prevention: Single oral *or intramuscular* vitamin K administration (1.0 mg) at birth is enough to prevent hemorrhagic disease in newborn, while periodic supplementation is necessary in chronic liver diseases and other deficiency states.

6.8 MINERAL DISORDERS AND TRACE ELEMENTS

Minerals are non-energy yielding micronutrients, which despite contributing <5% of body weight, play a vital role in human metabolism, health and disease. Minerals, along with other micronutrients, e.g. vitamins, are considered as responsible for *hidden hunger,* i.e. nutrient deficiencies without apparent manifestations in early stages.

Biologically important minerals may be broadly classified into:

- ***Macrominerals,*** which are present in substantial amounts with nutritional requirement usually exceeding >100 mg/day. Most of them are distributed in tissues as well as function as major electrolytes in body fluids, e.g. sodium, potassium, calcium, magnesium, etc. Important macrominerals have been discussed in Ch 7.
- ***Microminerals (trace elements),*** which constitute <250 µg/gm of body tissue matrix. Minerals present in still smaller amounts (<100 ng/gm) are termed as *ultra-trace elements*.

Role of trace elements in health and disease is being increasing recognized in recent years, which can be broadly divided into three categories, based on current knowledge:

1. *Essential trace elements with known biological functions*, e.g. iron, iodine, zinc, fluorine, selenium, copper, molybdenum and chromium.
2. *Essential trace elements with hitherto ill-identified functions*, e.g. manganese, silicon, nickel, boron, cobalt and vanadium.
3. *Potentially toxic trace elements with unknown biological functions,* e.g. lead, aluminum, tin, cadmium, arsenic, mercury, etc.

Table 6.20 presents an overview of important trace elements in human health and disease. While some of them have been discussed elsewhere, e.g. iron (Ch 19.4.1) and iodine (Ch 22.3.3), other important trace elements are discussed as follows:

Zinc is a component of many enzymes, e.g. carbonic anhydrase, carboxypeptidase, alkaline phosphatase, etc. Although widely distributed in tissues, average adult body contains <2–3 gm of zinc. Zinc deficiency is widely prevalent (~40–45%) in Indian children.

Physiology: Zinc is essential trace element for: (a) normal growth, (b) normal chemotaxis and T-cell immunity, (c) normal wound healing, and (d) synthesis of some hormones, e.g. insulin and nucleic acids. Zinc is not well conserved in body as there are no conventional tissue reserves.

RDA for zinc varies from 2.5 mg/day in infancy to ~15 mg/day in adolescents and adults.

Sources: Important sources of zinc include animal foods, e.g. meat, milk and fish, as well as plant foods, e.g. grains, legumes and nuts, though the bioavailability of zinc from plant sources in relatively poor.

Etiologically, zinc deficiency is rarely dietary, usually caused by:

- Increased requirements in early infancy, adolescents and pregnancy
- Decreased intake, e.g. in maternal zinc deficiency, total parenteral nutrition, etc.

TABLE 6.20: Essential trace elements at a glance

*Minerals (RDA)**	*Important functions*	*Deficiency states*	*Toxicity*
Iron (3–30 mg)	Heme synthesis (Hb, myoglobin) *Enzymes:* MAO, cytochrome oxidase	Anemia, growth failure Learning disabilities	Hemosiderosis Hemochromatosis
Iodine (90–140 mg)	Constituent of thyroid hormones	Goiter, Endemic cretinism	Goiter
Zinc (5–15 mg)	Constituent of metalloenzymes Wound healing	Acrodermatitis enteropathica Acquired deficiency	*Acute:* GIT upsets, seizures *Chr.:* Anemia, CNS signs
Fluorine (0.7–10 mg)	Bone mineralization Formation of dental enamel	Dental caries	Fluorosis
Selenium (10–50 µg)	Antioxidant *Enzyme:* Glutathione peroxidase	Keshan cardiomyopathy Arthritis, myositis	*Selenosis:* Loss of hair and nails Dental caries, garlic breath
Copper (30–80 µg/kg)	*Hematopoisis:* Iron utilization *Enzymes:* Tyrosinase, uriase Antioxidant	Anemia/neutropenia, Scurvy-like bone changes Recurrent diarrhea	Wilson's disease, ICC Menkey's disease Hemolytic anemia
Chromium (Not established)	Facilitates insulin action (co-factor)	? Hyperglycemia	Renal failure, dermatitis
Molybdenum (1.0–1.5 µg/kg)	*Enzyme: Xanthine oxidase*	Oral/esophageal cancers Seizures, mental retardation	Bony deformities Hyperuricemia
Cobalt (Not established)	Component of vit B_{12} & erythropoietin ? Iodine metabolism	? Hypothyroidism Anemia	Cardiomyopathy Goiter
Manganese (Not established)	Enzyme: Superoxidase dismutase	Failure to thrive, Skeletal abnormalities Reddening of hair	Encephalopathy
Nickel (Not established)	Membrane stabilizing effect *Enzyme: Urease*	Not known Nasal and lung cancers	Dermatitis, liver necrosis
Silicon (Not established)	Normal collagen formation	Not known, ? related to aging	Granuloma/fibrosis of lung
Boron (Not established)	Co-factor in steroid metabolism	Hypocalcemia, osteoporosis	Not known
Vanadium (Not established)	Sodium-potassium exchange	Not known	Not known

RDA: Recommended dietary allowance; **ICC:** Indian childhood cirrhosis

- Decreased absorption in:
  - Acrodermatitis enteropathica
  - Chronic diarrhea and malabsorptive states
- Increased urinary excretion in:
  - Chronic renal or liver disease
  - Hypoalbuminic states, e.g. kwashiorkor
  - Massive tissue injury, e.g. burns
  - Iron chelation therapy, e.g. in hemolytic anemia

Clinical features of zinc deficiency include:

- Failure to thrive, IUGR and hypogonadism
- Chronic diarrhea and anorexia
- Eczematous skin lesions and alopecia
- Increased infections and delayed wound healing.

Acrodermatitis enteropathica is an autosomal recessive defect in zinc absorption due to defective zinc transporter protein (ZIP4), which usually manifests during or after weaning with: (a) growth failure, (b) chronic diarrhea, (c) eczematous skin lesions, mainly on acral (hands/feet), inguinal and/or flexural parts of body, and (d) alopecia.

Diagnosis is confirmed on serum zinc estimation (N:6.6–19.4 µg/ml) and response to therapy.

Treatment: Oral or parenteral supplementation with 5 mg/kg/day (20–40 mg/kg/d in acrodermatitis enteropathica) usually leads to dramatic clinical response within a few days, which should be followed by adequate dietary modification to prevent recurrence. Long-term zinc supplementation is indicated in children with severe growth failure and acrodermatitis enteropathica.

Zinc supplementation is also indicated for 2 weeks in all children with – severe acute malnutrition (2 mg/kg/day) and diarrheal disorders (20 mg/day or 10 mg/day in infants < 6 months). It is also recommended as adjunct therapy in preterms (2 mg/kg/d for 3 months) and haemolytic anemia, e.g. sickle cell disease or thalassemia.

Fluorine is the most abundant element in nature, though never found in free elemental gaseous form. About 96% of body fluorine is present in bones and teeth.

Physiologically, fluorine is required for formation of *apatite*—a mineral complex essential for bone mineralization and dental enamel.

Sources: Drinking water is the principle source of fluorine to man apart from sea-food and cheese as other rich sources.

Fluorine deficiency is relatively uncommon, considered to be associated with higher incidence of dental caries and can be prevented by use of fluorinated toothpastes.

Fluorine excess (fluorosis) is more important public health problem in India, endemic in areas with high fluoride content in drinking water (>0.5–0.8 mg/L or >2 ppm).

Prolonged ingestion of high-fluoride water presents with: (a) mottling of teeth, (b) brittle bones with osteosclerosis, (c) calcification of muscles/tendons, and (d) failure to thrive, anemia and asthenia. As excess fluorine interferes with calcium metabolism, co-existing calcium deficiency is common and contributes to skeletal changes with osteoporosis/osteomalacia.

Controlling the fluoride content of drinking water is the only method to prevent fluorosis in children.

Copper: Nearly 60% of copper is present within erythrocytes, rest being in plasma (bound to ceruloplasmin) or tissues (bound to metallothionein).

Physiologically, copper is a constituent of many metabolic enzymes, involved in connective tissue formation, iron metabolism, neuronal myelination, melanin synthesis and cellular energy/oxygen utilization.

Copper deficiency is rarely dietary, presenting as neutropenia, microcytic hypochromic anemia, hypopigmented hair, osteoporosis and defective immune function.

Copper toxicity, usually due to use of copper cooking utensils and has been implicated in Indian childhood cirrhosis and hematological malignancies.

Inborn errors of copper metabolism are most important cause of altered copper status in body and include:

- *Wilson disease*—an autosomal recessive defect in mobilization of hepatic copper, presenting with a triad of chronic liver disease, extra-pyramidal signs and Kayser-Fleischer ring over cornea (Chapter 15.7).
- *Menkes-kinky-hair syndrome*—a rare X-linked recessive disorder, characterized by fine, brittle and light colored hair, progressive psychomotor retardation and hypopigmented skin.

Selenium is mainly required for: (a) synthesis of *glutathione peroxidase*, an important anti-oxidant enzyme, and (b) conversion of T4 into T3.

Selenium deficiency is definitely associated in two endemic diseases in China— *Keshan cardiomyopathy* and *Kaschin-Beck osteoarthritis*. It has been also implicated in higher risk for malignancies and atherosclerosis. Selenium deficiency may affect growth and development due to poor conversion of T4 into T3.

Selenium excess (selenosis) is associated with alopecia and nail deformities.

Molybdenum is a constituent of many enzymes, specially xanthine oxidase and xanthine dehydrogenase-essential for xanthine metabolism.

Molybdenum deficiency is mainly seen in children on prolonged total parenteral nutrition, presenting with renal calculi (due to xanthinuria) and myopathy. It has been also implicated in higher risk of dental caries an esophageal cancers.

Chromium: Major biological role of chromium is to potentiate the action of insulin in carbohydrate, lipid and protein metabolism, probably by acting as a glucose tolerance factor.

Chromium deficiency has been reported only in children on prolonged total parenteral nutrition, leading to impaired glucose tolerance and hyperglycemia. Dietary chromium supplementation may improve glucose tolerance in malnutrition.

6.9 FREE RADICALS IN HEALTH AND DISEASE

Free radicals, i.e. *atoms or molecules with one or more unpaired electrons in their outermost orbits*, are regularly formed in body during normal metabolic activity and eliminated by various antioxidant mechanisms. Excess production *or* inadequate elimination of these radicals has been recently identified as an important contributor in cellular aging, disease and death.

Three most important free radicals in human context are: *singlet oxygen* (O^-), *superoxide* and *peroxide* anions and *hydroxyl* radicals.

Sources: Free radical excess is implicated to:

- *Exogenous or environmental sources*, e.g. smoke, air pollutants, radiation, ultraviolet rays, etc. or
- *Endogenous or metabolic sources*, e.g. infections, cellular ischemia/hypoxia, toxic tissue injury.

Antioxidants: Important antioxidant substances in body may be broadly divided into three categories:

a. *Metabolic enzymes*, e.g. superoxidase mutase, catalase, glutathione peroxidase, etc.
b. *Metal ion chelators*, e.g. plasma proteins, transferrin, ceruloplasmin, etc.
c. *Oxygen scavengers*, e.g. vitamins (A, E, C) and minerals (selenium, zinc).

Pathology: Free radical tissue injury is considered as an important cause of *altered cellular permeability and metabolism*, leading to early cell death in innumerable disease processes, including:

- Hyperoximia-related problems in preterms, e.g. retinopathy of prematurity or bronchopulmonary dysplasia,
- Hypoxic-ischemic injuries, e.g. neonatal enterocolitis, hypoxic-ischemic encephalopathy,
- Sepsis/septic shock,

- Metabolic disorders, e.g. kwashiorkor, Wilson disease, hemochromatosis, etc.,
- Hemolytic anemia or malignancies, and
- Premature atherosclerosis or aging in adults, etc.

Prevention of free radical injury depends on avoidance of environmental risk factors, early treatment of primary disease and adequate consumption of natural antioxidants, i.e. vitamins and minerals. Consumption of fruits and vegetables (400 gm/day) is considered as adequate to minimize free radical injury.

Treatment: Recently, many synthetic antioxidants have been used in selected cases of suspected free radical injury, e.g. *xanthine oxidase inhibitors*, e.g. allopurinol, *N-acetylcysteine*, *recombinant enzymes*, e.g. glutathione peroxidase analogues, superoxide dismutase, coenzyme Q derivatives, etc. or *natural antioxidants* (as above), with equivocal results.

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CHAPTER

7

Fluid and Electrolyte Balance

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Fluid and electrolyte composition of body is in a state of dynamic balance, regulated by various inter-related mechanisms. Understanding of these mechanisms and their abnormalities is essential for rational fluid and electrolyte therapy in sick children.

7.1 WATER HOMEOSTASIS

Total body water (TBW) contributes to ~78% of body weight at birth, but declines rapidly due to physiological diuresis in newborns and growth of adipose tissue in late infancy, to reach the adult level of ~55–60% by *one year* of age. Post-pubertal females and obese persons have relatively less body water due to excess fat accumulation. In non-obese children, TBW may be calculated as:

TBW (Liters) = 0.61 Body weight in kg + 0.251.

TBW is distributed into four body compartments:

a. *Extracellular compartment* or ECF (20–25%) as plasma (5%) and interstitial fluid (15%).
b. *Intracellular compartment* or ICF (30–40%).
c. *Transcellular water* (2%) as urine, gut secretions, CSF and body cavity fluids.
d. *Slowly exchangeable fluid compartment* in bones, cartilages and connective tissue.

At birth, ECF is more than ICF, but this ratio is reversed by the end of infancy due to postnatal diuresis and cellular growth. Transcellular water and water in slowly exchangeable fluid compartments, though important metabolically, does not play significant role in water homeostasis.

7.1.1 PHYSIOLOGY OF WATER BALANCE

Physiology of water balance may be broadly divided into: (a) overall quantitative regulation of TBW, and (b) its inter-compartmental distribution, as follows:

A. TBW homeostasis revolves around the maintenance of normal plasma volume and osmolality. *Volume* of the TBW depends on the equilibrium between external intake and small amount produced endogenously on oxidation of nutrients on one side; and excretion via urine (65%), skin (40%), lungs (15%) and stools (5%) on other side.

Osmolality of the plasma depends on the pressure exerted by its two components: (a) *colloids*, e.g. albumin, and (b) *crystalloids* or electrolytes, e.g. Na^+ and Cl^-. Though colloidal (oncotic) pressure contributes only to a small fraction of total plasma osmotic pressure, it is more important determinant of osmotic gradient across the cell membranes than crystalloid pressure, as colloids do not pass through cell membranes.

The terms *molality* and *molarity* refers to number of solute molecules in 1 kg and 1 liter of solvent, respectively. Accordingly, *osmolality* refers to the 'pressure exerted by number of molecules in 1 kg of solvent', while *osmolarity* denotes 'molecular pressure in 1 liter of solvent'. Normal plasma osmolality (285–295 mOsm/kg H_2O) roughly equals to the twice of plasma sodium concentration in mEq/L, though may be precisely calculated by following formula:

$$\text{Osmolality} = 2\,(Na^+ + K^+) + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{2.8}$$

Osmolality in mOsm/kg; Na/K in mEq/L; glucose/BUN in mg/dl.

Important regulatory mechanisms for TBW balance in human body **(Fig. 7.1)** are as follows:

a. Water intake depends on *thirst*, i.e. conscious desire to drink water, which is regulated by a center in mid-hypothalamus with two important afferents: *Osmoreceptors* in hypothalamus to detect changes in plasma osmolality and *baroreceptors* in atria and vascular bed to sense changes in plasma volume. Probably, elevated angiotensin II levels in hypovolemic states also stimulate thirst.

Primary disorders of thirst, i.e. *polydipsia* or *adipsia* are usually psychogenic in origin, though altered thirst may also indicate hypothalamic disorders, hypokalemia, malnutrition and disorders of renin-angiotensin system.

b. Urinary excretion is the most important determinant of TBW regulation. A part of urinary water excretion is *obligatory*, necessary to excrete the solute load. However beyond this, urinary volume is regulated by: (a) plasma

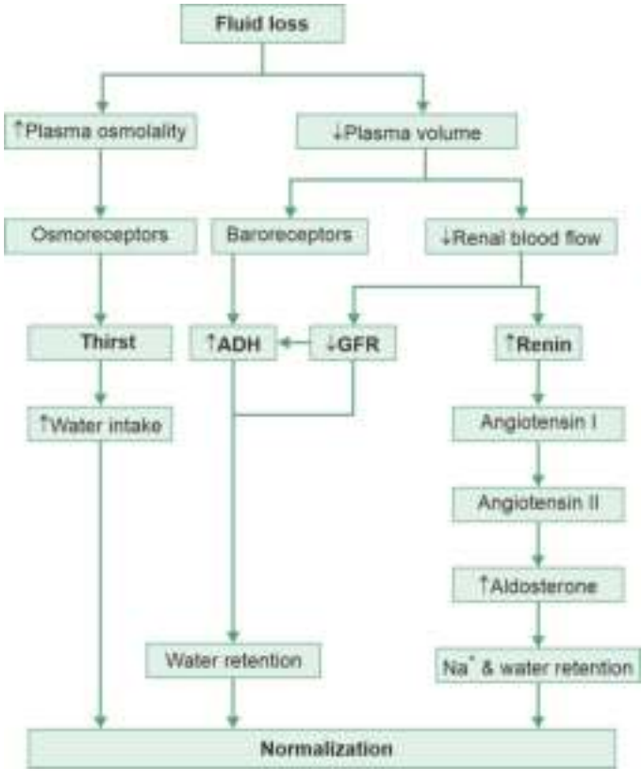

Fig. 7.1: Physiology of total body water balance.

volume and osmolality, (b) dietary solute load, (c) renal functions, and (d) hormonal control. Three important hormonal regulators of urinary water excretion are antidiuretic hormone (ADH), aldosterone and atrial natriuretic hormone peptide.

- *Antidiuretic hormone* of hypothalamic-hypophyseal axis, is a direct regulator of urinary water excretion. ADH secretion is regulated by osmotic pressure of ECF and it acts by increasing the cell-permeability of collecting ducts to enhance water absorption.

  Important ADH disorders include: (a) excess secretion in neurological disorders, i.e. syndrome of inappropriate secretion *or* SIADH, (b) ADH deficiency in central diabetes insipidus, and (c) tubular non-responsiveness to ADH in nephrogenic diabetes insipidus (Ch 22.2.4).
- *Aldosterone, a*n adrenal hormone, is an indirect regulator of urinary water excretion, by manipulating sodium excretion. It is mainly secreted in response to reduced plasma volume via renin-angiotensin mechanism and increases tubular sodium reabsorption with *passive* water absorption.
- *Atrial natriuretic hormone peptide* is produced and stored in atrial myocytes and released in response to ECF overload leading to atrial stretching. It prevents the sodium/water reabsorption by antagonizing the renin-angiotensin mechanism.

TABLE 7.1: Major ions in body fluids

	Plasma	*Interstitial fluid*	*ICF*
Cations			
Sodium	**142**	**144**	6
Potassium	5	5	**154**
Magnesium	3	5	40
Anions			
Bicarbonates	24	27	13
Chlorides	**105**	**118**	–
Proteins	15	–	60
Phosphates	5	5	**106**

Figures in bold indicate major cation/anion in respective fluid compartments

c. Non-urinary losses in stools or insensible losses via skin/lungs are fairly constant in normal children with a little influence on overall water balance. However, these are important exits in pathological states, e.g. diarrhea (stools), fever (skin), respiratory distress (lungs). Insensible losses are also influenced by environmental temperature, humidity and body surface area, which should be considered during calculation of fluid requirements in sick children.

B. Inter-compartmental distribution: Water in ECF and ICF compartments is freely exchangeable and exists in a state of dynamic equilibrium. Within ECF too, water continuously moves between plasma to interstitial fluids. Important determinants of these inter-compartmental water distributions are as follows:

Extracellular *vs* intracellular fluid: Water movement between these two compartments depends on the relative osmotic gradient and active movement of ions. While *sodium is the principle cation in ECF, potassium is principle cation in ICF* **(Table 7.1)**. Since cell membranes are free permeable to water, osmotic force across them is maintained by active transport of Na^+ out of the cell and K^+ into the cell-an energy-consuming process. Any change in Na^+ content of ECF alters its osmolality with secondary effects in ICF. For example, hypernatremia increases osmolality of ECF> movement of water from ICF to ECF> cellular dehydration. Conversely, hyponatremia leads to movement of water into the cell and consequent cellular edema.

Plasma *vs* interstitial fluid: Interstitial fluid is derived from plasma, filtered through the semi-permeable capillary bed at the arteriolar end. However, most of it returns back to plasma at venular end, while the rest is carried back to vascular space via lymphatics. Important determinants of fluid movements between plasma and interstitium are:

- *Hydrostatic pressure* in capillary bed that facilitates water movement from plasma to interstitial space;
- *Osmotic pressure* of plasma that prevents or reverts this movement; and
- *Capillary permeability*.

In normal conditions, osmotic gradient between plasma and interstitial space (28 – 4.5 = 23.5 mm Hg) and capillary permeability is virtually constant, and water movement between these compartments is mainly decided by hydrostatic pressure, as follows:

- *At the arteriolar end* of capillary bed, hydrostatic pressure is more in vascular space than in interstitial space. Consequently, net hydrostatic pressure gradient (25 – (–7) = 32 mm Hg) exceeds osmotic gradient (23.5 mm Hg) and water moves out into interstitial spaces.
- *At venular end,* hydrostatic pressure in vascular space drops to 9 mm Hg. Consequently, net hydrostatic pressure gradient (9 – (–7) = 16 mm Hg) is less than osmotic gradient and water moves back in vascular space. Some interstitial fluid is collected by lymphatics, ultimately to return in vascular compartment.

Two important pathological abnormalities of fluid imbalance in children are edema and dehydration, discussed in following sections.

7.1.2 EDEMA

Edema is a clinical term to denote *excess accumulation of fluids in interstitial fluid compartment*, which normally contributes to ~15% of TBW.

Etiology: Edema is caused by any factor that: (a) reduces plasma oncotic pressure, (b) increases hydrostatic pressure, (c) increases capillary permeability, and (d) prevents lymphatic return **(Table 7.2)**.

Diagnostic approach: Although the edema *per se* is a clinical diagnosis, etiological diagnosis requires detailed history, clinical examination and relevant investigations. Important differentiating features of edema include:

- ***Onset:*** Allergic *or* toxic edema due to increased capillary permeability develops rapidly within a few hours, while other causes lead to gradual and progressive edema.
- ***Distribution:*** Generalized edema is usually nutritional, renal or cardiac in origin. Renal edema typically begins from face as periorbital puffiness, while cardiac or nutritional edema is most prominent over dependent parts, e.g. legs in older children and sacrum in infants.

  Localized edema is seen in: (a) lymphatic obstruction, (b) allergic conditions, e.g. angioneurotic edema, (c) localized vascular compressions, and (d) early stages of generalized edema.
- ***Diurnal variation:*** Renal edema is maximum in morning due to overnight fluid retention, while cardiac edema is more prominent in evening due to gradual decompensation after physical activity.
- ***Pitting vs. non-pitting edema:*** While severe edema is grossly visible, presence of mild/moderate edema may be confirmed by compressing on a bony part, e.g. shin of the tibia for >10 sec. Pitting subcutaneous edema indicates interstitial fluid accumulation.

  Non-pitting edema is rare in children, seen in: (a) hypothyroidism or myxedema, (b) obesity, and (c) long-standing edema with secondary changes, e.g. lymphatic filariasis.
- ***Co-existing features*** of primary disease also help in differential diagnosis, e.g. itching (allergic causes), jaundice (hepatic disease), anuria/oliguria (renal disease), cardiac signs, etc.

TABLE 7.2: Causes of edema

a. Reduced oncotic pressure *(hypoproteinemia)*
- Nutritional kwashiorkor (↓ intake)
- Malabsoprtion syndrome (↓ absorption)
- Chronic liver disease (↓ synthesis)
- Nephrotic syndrome (↑ renal loss)
- Protein-losing enteropathies (GIT loss)
- Burns (↑ skin loss)
- Pleural effusion/peritonitis (third space loss)

b. Increased hydrostatic pressure
- *Cardiac:* CCF, pericarditis, hypertension
- *Extra-cardiac:* Budd-Chiari syndrome, mediastinal mass
- *Water retention:* Renal failure, steroids, fluid overload

c. Increased capillary permeability
- *Allergic:* Urticaria, angioneurotic edema
- *Toxic:* Septicemia, epidemic dropsy
- *Inflammatory:* Infections, burns

d. Lymphatic obstruction
- *Congenital anomalies:* Lymphangioma
- *Acquired:* Filariasis, traumatic, surgical

7.1.3 DEHYDRATION

Dehydration denotes *loss of TBW from extracellular and/or intracellular compartments*, due to reduced intake *or* more likely, excessive losses via urine, stools, lungs or skin. As these losses are predominantly from ECF compartment, ECF dehydration dominates in early stages. ICF dehydration usually develops after redistribution of fluids.

Etiology: Acute diarrhea *and/or* vomiting is the commonest cause of dehydration in children, apart from other causes, listed in **Table 7.3**.

Pathogenesis: As water loss is almost always associated with loss of other electrolytes, specially sodium, pathophysiological changes in dehydration can be broadly divided into three categories:

a. ***Isonatremic dehydration*** (50%), i.e. proportionate loss of water and sodium, e.g. in osmotic diarrhea, with *normal* serum osmolality. In established isotonic dehydration, usually 60% of fluid loss is from ECF and remaining 40% is from ICF.

b. ***Hyponatremic dehydration*** (30–40%), i.e. disproportionately higher loss of sodium than water, e.g. in secretory diarrhea. Serum osmolality falls with consequent movement of water from ECF to ICF,

TABLE 7.3: Common causes of dehydration

a. Excessive losses
- *GIT:* Diarrhea, vomiting, gastric aspiration
- *Urine:* Polyuria (e.g. diabetes insipidus)
- *Lungs:* Tachypnea (respiratory disorders)
- *Skin:* Fever, excessive sweating, burns
- *Third-space losses:* Paralytic ileus, gross ascites

b. Poor intake
- Unconscious/sick child
- Starvation
- Psychogenic

c. Re-distribution of fluids
- Edema (intravascular > interstitial fluid)
- Hyperosmolar states, e.g. DKA (ECF > ICF)

DKA: Diabetic ketoacidosis

leading to: (a) further depletion of ECF, and (b) cellular overhydration, e.g. cerebral edema. Clinical signs of dehydration in these cases are disproportionately more than the estimated fluid loss.

c. ***Hypernatremic dehydration*** is rare (<5%), usually attributed to erroneous fluid therapy with concentrated oral rehydration fluids or hypertonic parenteral fluids. In these cases, higher serum osmolality leads to movement of water from ICF to ECF with: (a) partial compensation of ECF loss by ICF fluids, and (b) cellular dehydration. Signs of dehydration in these cases are disproportionately less than estimated fluid loss.

Clinical features of dehydration depend on its severity and indicate:
- *Compensatory mechanisms* to restore/conserve body water, e.g. excessive thirst, oliguria, dry skin/mucus membranes, etc.;
- *Circulatory decompensation*, e.g. weak and thready pulse, hypotension and shock; and
- *Cellular dehydration*, e.g. loss of skin turgor and mental changes.

Important clinical indicators of the severity of dehydration are given in **Table 7.4**.

Severity of dehydration is likely to be overestimated in marasmic children due to severe wasting (confused with turgor) or underestimated in obese children or kwashiorkor. *Urine output is the most reliable indicator in these cases.* Severity may also be misinterpreted in cases with hyponatremic or hypernatremic dehydration, as discussed earlier.

Hypernatremic dehydration is characterized by: (a) typical doughy skin, and (b) excessive irritability, rather than drowsiness in iso-/hypo-natremic dehydration.

Laboratory evaluation: Although clinical signs are cornerstones to evaluate the presence and severity of dehydration, following investigations are essential at least in severe cases to assess co-existing electrolyte imbalance and renal dysfunction.

TABLE 7.4: Severity assessment of dehydration

Feature	*Mild*	*Moderate*	*Severe*
Behavior*	Alert	Drowsy	Stupor/coma
Thirst	Thirsty	Marked	Absent
Eyeballs	N	Sunken	Sunken
Tears	Present	Absent	Absent
Tongue	Dry	Dry	Parchmenty
Skin turgor	N	Lost**	Lost
Pulse	N	Rapid	Thready
Respiration	N	Rapid	Acidotic
BP	N	N	Hypotension
Urine output	N	Oliguria	Anuria
Wt loss (<1 yr)	~ 5%	~ 10%	~ 15%
Wt loss (>1 yr)	~ 3%	~ 6%	~ 9%

*Irritable in hypernatremic dehydration
**Doughy feel in hypernatremic dehydration.

- Serum electrolytes, e.g. Na^+, K^+, HCO_3^- and Cl^-,
- Renal parameters, e.g. blood urea, serum creatinine.
- Urinalysis, including specific gravity.
- Hemogram including hematocrit.
- Relevant etiological investigations.

Management of dehydration involves oral or parenteral fluid therapy. While oral fluid therapy is discussed in Ch 14.10, general principles of parenteral fluid therapy are discussed in Ch 7.7.

7.2 SODIUM DISORDERS

Sodium is the principle *cation* in extracellular fluid, responsible for maintenance of osmolality in intravascular and interstitial fluid compartments. About 45% of total body sodium is present in body fluids, rest being in bones, cartilages and connective tissues. Most of the tissue sodium is not in exchangeable form, with limited role in sodium homeostasis. *Normal serum sodium concentration is 135–145 mEq/L.*

Physiology: Kidney is the prime regulator of sodium balance in body. While sodium is freely filtered through glomeruli, ~2/3rd of it is reabsorbed in proximal tubules and loop of Henle. Remaining sodium is also reabsorbed in distal tubules and collecting ducts and only <1% of filtered sodium is actually excreted in urine. Renal reabsorption of sodium is an active process, facilitated by renin-angiotensin mechanism and aldosterone secretion; and opposed by the atrial natriuretic hormone.

Hyponatremia is the commonest electrolyte abnormality in hospitalized children, defined as *S. sodium levels <135 mEq/L*, though it is rarely symptomatic till levels fall <125 mEq/L.

Causes: Gastrointestinal loss in diarrhea or vomiting is the commonest caus of hyponatremia in children, apart from other causes **(Table 7.5)**. In critically sick

TABLE 7.5: Causes of hyponatremia

Primary sodium deficit:
Extra-renal losses
GIT: Diarrhea, vomiting, nasogastric drainage
Skin: Burns, cystic fibrosis
Third space: Paralytic ileus
Renal losses
Prematurity: Poor concentration capability
Forced diuresis: Diuretics, diabetes mellitus
Renal: Renal tubular acidosis, acute tubular necrosis
Adrenal: Congenital adrenal hyperplasia (salt-loosing)
Disproportionate water retention:
Syndrome of inappropriate ADH secretion (SIADH)
Excess intake: Psychogenic, Na^+ free IV fluids
Renal: Nephrotic syndrome, renal failure
Congestive cardiac failure
Pseudo-hyponatremia *due to hyperlipidemia*
Nephrotic syndrome
Diabetic ketoacidosis

TABLE 7.6: Causes of hypernatremia

Increased sodium intake:
- Concentrated ORS or formula feeds
- Hypertonic IV fluids
- Near-drowning in sea water
- Use of common salt for emesis
- Intentional salt poisoning

Relative water deficit:
- Diabetes insipidus
- Diabetes mellitus
- Gastroenteritis
- Reduced oral intake—intentional, psychogenic
- Increased insensible loss—respiratory distress

children, excess ADH secretion, i.e. SIADH, may lead to disproportionate water reabsorption from kidneys and *dilutional hyponatremia.*

Etiologically, hyponatremia is also classified as:

- *Hypovolemic hyponatremia* with sodium loss in excess of the fluid loss due to renal or extrarenal losses;
- *Normovolemic or euvolemic hyponatremia* with proportionate loss of sodium and water, e.g. in SIADH or due to drugs, e.g. cyclophosphamide, vincristine, carbamazepine, etc;
- *Hypervolemic hyponatremia* due to excess water retention, e.g. in CCF, nephritic syndrome, cirrhosis, renal failure, etc.

Pathophysiology: Hyponatremia leads to decreased ECF osmolarity and consequent movement of water from ECF to ICF, leading to cellular edema including cerebral edema. Brain also attempts to adapt hyponatremia by extrusion of intracellular electrolytes and osmolytes (glutamine, aspartate, etc.), which are neuroexcitatory and can produce seizures, even without cerebral edema.

Clinically, symptomatic hyponatremia predominantly presents with signs of cerebral edema, e.g. altered sensorium and seizures. Severe cases may also present with hypertension, pulmonary edema and heart failure.

Hyponatremic encephalopathy is relatively more common in children than adults due to larger brain size (versus intracranial volume) and may lead to irreversible brain damage, if left untreated.

Asymptomatic prolonged hyponatremia in preterms may lead to poor growth, development and sensorineural hearing loss.

Treatment of hyponatremia depends on the cause, severity and duration:

- *Asymptomatic or dilutional hypernatremia,* e.g. in SIADH, does not require specific correction except fluid restriction and treatment of primary cause.
- *Acute symptomatic hyponatremia* should be treated with IV 3% NaCl as a bolus of 2 ml/kg over 10–15 minutes (or 3–5 ml/kg over first hour), which may be repeated to maximum 100 ml, till the symptoms resolve. Serum sodium level should be monitored every 2 hours, with an objective to raise them by ~5–6 mEq/L in first 1–2 hours.
- *Chronic or left-over hyponatremia after acute correction* should be treated more slowly with IV 3% NaCl, in doses calculated with following formula:

  Sodium deficit (mEq) = (125 – actual S. sodium) × body weight × 0.6

  Whereas 125 is desired Na^+ level and 0.6 is distribution coefficient of sodium in body.

Rapid correction of hyponatremia should be avoided to prevent pontine/ extra-pontine osmotic myelinolysis, once serum sodium levels approach 125 mEq/L and no more than 10 mEq/L deficit should be corrected in 24 hours. As a thumb rule, 12 ml/kg of 3% NaCl raises S. Na^+ levels by ~10 mEq/L.

Hypernatremia is relatively less common than hyponatremia, defined as serum sodium levels >145 mEq/L.

Causes: Hypernatremia in children is usually *iatrogenic* in origin, due to use of concentrated oral rehydration/ parenteral fluids. *Concentration hypernatremia* is seen in disorders with excessive water loss, e.g. diabetes insipidus **(Table 7.6)**.

Pathophysiology: Hypernatremia increases osmolarity of the ECF, leading to movement of water from ICF to ECF and consequent cellular dehydration. In acute severe hypernatremia, this osmotic shift may lead to shrinkage of the brain, tearing of meningeal vessels and intracranial hemorrhage.

Clinically hypernatremia present with features of cellular dehydration. Increased thirst is the earliest compensatory response and clinical indicator to developing hypernatremia, followed by:

- *Neurological* signs, e.g. irritability, twitching and seizures.
- *Skin* signs, e.g. dry skin with typical doughy consistency, which may mask signs of dehydration.

Thrombotic complications due to intracellular dehydration and consequent hypercoagulability may develop in severe cases, including strokes, renal vein thrombosis and deep vein thrombosis.

Investigations: All cases of hypernatremia should be assessed for serum and urine osmolality and urinary sodium, along with blood urea, serum creatinine and electrolytes. Neuroimaging for intracranial pathologies and hormonal assays for endocrinal causes, e.g. serum aldosterone, cortisol, ADH and ACTH may be necessary in cases with occult etiology.

Treatment: Hypernatremia is generally well tolerated as brain generates idiogenic osmols to increase the intracellular osmolarity. Rapid correction of hypernatremia should be avoided to prevent sudden decrease in ECF osmolarity, which may lead to rapid movement of water within the cells and consequently cause cerebral edema with seizures, pulmonary edema and congestive cardiac failure. As general rule, *the rate of sodium correction should never exceed 0.3–0.5 mEq/L per hour or 8–12 mEq/L per day.*

Important considerations in correction of hypernatremia include:

- Recommended IV fluid is N/2 saline in DW 5% (with added 20 mEq/KCl after passage of urine). Sodium-free fluids should *never* be used to avoid rapid correction.
- Replacement fluid volume should be ~1.5 times of maintenance requirement + deficit correction as 3–4 ml/kg for each mEq/L of serum Na^+ above 145 mEq/L, infused over recommended period. Ongoing losses should be added as required. Oral rehydration should be started as early as possible.
- Sodium levels should be monitored every 1–2 hourly to limit the rate of fall <0.5 mEq/L/hour.
- If child develops seizures due to rapid correction, administer 3% Nacl 4–6 ml/kg over 30 minutes.
- Peritoneal dialysis is indicated for serum Na^+ exceeds 180 mEq/L, using high glucose-low sodium dialysate.
- In cases presenting with hypotension/shock on admission, hypernatremic correction should start after one or two boluses of 20 ml/kg. Normal saline over 20 minutes for restoration of intravascular volume.

7.3 POTASSIUM DISORDERS

Potassium is the principle *intracellular* cation, essential to maintain resting membrane potential of cells (along with major extracellular cation - sodium) and consequently, adequate excitability of neurons and contractility of muscles.

Normal serum potassium levels are 3–5 mEq/L. More than 90% of potassium is present in body fluids, rest being in bones, cartilages and connective tissue.

Physiology: Dietary intake of potassium is usually adequate and rarely affects serum potassium levels. Maintenance of normokalemia mainly depends on:

- Renal excretion, regulated by serum K^+ levels, blood pH and hormones, e.g. aldosterone.
- Transcellular movements during blood pH changes- Potassium moves out of the cell during acidosis (leading to ECF hyperkalemia) and into the cell during alkalosis (leading to ECF hypokalemia).

Hypokalemia is the commonest electrolyte abnormality in sick children, defined as *S. potassium levels <3 mEq/L.*

Causes: Severe diarrhea or vomiting is the commonest cause of acute hypokalemia, while persistent hypokalemia usually indicates underlying renal disease **(Table 7.7)**.

Pathophysiology: Low extracellular potassium levels slow down the post-depolarization return of potassium into the cells, delaying process of repolarization and leading to impaired neuromuscular excitability.

Clinically, hypokalemia presents with signs of impaired neuromuscular excitability, as follows:

- *Skeletal muscle involvement*, e.g. limb weakness, hypotonia, hyporeflexia, abdominal distension and respiratory muscle paralysis. Rhabdomyolysis is a rare but important complication.
- *Smooth muscle involvement*, e.g. paralytic ileus, orthostatic hypotension, bradyarrhythmia.
- *Characteristic ECG changes*, which may precede clinical features in hypokalemia and include: (a) low voltage, (b) ST depression with flat/inverted T waves, (c) prolonged QTc interval, and (d) prominent U waves.

Prolonged hypokalemia also affects renal concentration capability, manifesting as polyuria, polydipsia, metabolic alkalosis *with* secondary failure to thrive and nephrosclerosis.

Treatment: *Symptomatic* **or** *severe* hypokalemia (<2.5 mEq/L) must be treated with slow potassium chloride infusion (2 mEq/ml) in IV fluids as 0.5–1 mEq/kg over

TABLE 7.7: Causes of hypokalemia

a. Extrinsic losses:
- *GIT:* Diarrhea, vomiting, nasogastric drainage
- *Urinary*:*
  Renal: Renal tubular acidosis, Bartter syndrome
  Endocrinal: Cushing syndrome, hyperaldosteronism
  Iatrogenic: Diuretics, *e.g.* furosemide
  Metabolic: Diabetic ketoacidosis
- *Skin:* Profuse sweating
- ↓ *muscle mass:* Severe malnutrition

b. Transcellular redistribution**
- Alkalosis/rapid correction of metabolic acidosis

c. **Others:** Familial hypokalemic periodic paralysis

*Urinary K^+ <15 mEq/L indicate extra-renal loss of potassium.
**In acidosis, K^+ moves out of the cell. Rapid correction leads to return of K^+ intracellularly, causing hypokalemia.

1–2 hours, with monitoring every 2–4 hours. Potassium concentration in the infusate should never exceed 60 mEq/L.

Prolonged hypokalemia due to renal diseases or diuretics may be prevented or treated with oral potassium chloride (20 mEq/15 ml) given as 2–4 mEq/kg/day, along with treatment of primary cause.

Hyperkalemia is defined as *S. potassium levels >5.5 mEq/L.* Serum potassium levels of >8.5 mEq/L are often fatal.

Causes: Acute renal failure is the commonest cause of hyperkalemia in children, apart from other causes given in **Table 7.8**.

Pathophysiology: High ECF potassium in hyperkalemia resists further efflux of potassium from the cells during depolarization, leading to slow membrane depolarization.

Clinically, these cases present with signs of neuromuscular irritability, as follows:

- *Neurological signs*, e.g. muscular weakness, paresthesia, tetany, etc.
- *Cardiac signs*, e.g. bradycardia, shock and tachyarrhythmia.
- *Characteristic ECG changes* in hyperkalemia may precede clinical features and often correlate with serum potassium levels, including: (a) peaked *'tented'* T waves, (b) prolonged PR interval, (c) wide QRS complexes, and (d) flat or absent p waves in severe cases.

Treatment of hyperkalemia is an *emergency* in cases with serum levels >6.5 mEq/L or presence of ECG changes and must be treated with:

- Discontinuation of all potassium containing fluids and medications;
- IV calcium gluconate 10% (0.5–1 ml/kg) with cardiac monitoring to stabilize myocardial cell membrane and counteract cardiac toxicity of potassium.
- IV insulin infusion (0.3 U/kg) in 1 ml/kg of DW50% over 1 hour to enhance cellular uptake of potassium, co-transported with glucose.

TABLE 7.8: Causes of hyperkalemia

a. Decreased renal excretion
- Acute/chronic renal failure
- Hypoaldosteronism, salt-loosing CAH
- Use of potassium-sparing diuretics

b. Increased intake
- *Iatrogenic:* Potassium salts, penicillin
- Blood transfusions (sp. old blood)

c. Hypercatabolic states *(release from tissues)*
- *Medical:* Burns, *tumor lysis syndrome**
- *Surgical:* Extensive trauma, major surgery

d. Transcellular distribution**
- Metabolic acidosis
- Familial hyperkalemic periodic paralysis

e. Pseudohyperkalemia: Hemolysed sample

*during chemotherapy, ** shift of K^+ out of the cells.

- IV sodium bicarbonate (1–2 mEq/L over 30 min), to create an alkalotic state that facilitates re-entry of potassium into the cells.
- Dialysis in cases of refractory *or* life-threatening hyperkalemia, e.g. in acute renal failure or tumor-lysis syndrome.
- *Prolonged mild/moderate hyperkalemia*, e.g. in chronic renal disease/failure, may be treated with ion exchange resins, e.g. kayexalate or sodium polystyrene sulfonate given orally or rectally as 1 gm/kg/dose (Max 15 gm).

7.4 CALCIUM DISORDERS

Bones are main reservoir of calcium, containing ~99% of total body calcium. Normal plasma calcium level is *9–11 mg/dl*, which is ~60% is in *bound form* with albumin or other anions, e.g. phosphates, and the rest in *free ionic form* (4.0–5.2 mg/dl).

Calcium in extracellular fluids is in equilibrium with skeletal calcium and plays vital role in many physiological processes, e.g. neuromuscular transmission, coagulation and cellular functions. Calcium affects cellular functions through it binding regulatory protein – *calmodulin*.

RDA for calcium varies with age as 300 mg/day in infants, 500–600 mg/day in children and ~1000 mg/day in adolescents.

Sources: Dairy products are most important source of calcium along with millets, e.g. ragi and root vegetables, e.g. tapioca. Cow milk has more calcium than breast milk (1200 mg/dl *vs* 300 mg/dl), though later is absorbed better than former. Presence of phytates, oxalates and citrates in diet inhibits its absorption.

Physiology: Calcium homeostasis largely depends on renal reabsorption, mobilization from bones and intestinal absorption, regulated by various hormones, e.g. parathormone, vitamin D and calcitonin, as follows, **(Fig. 7.2)**:

- *Parathyroid hormone* (PTH) increases S. Ca^{++} levels by facilitating its absorption from gut, reabsorption from

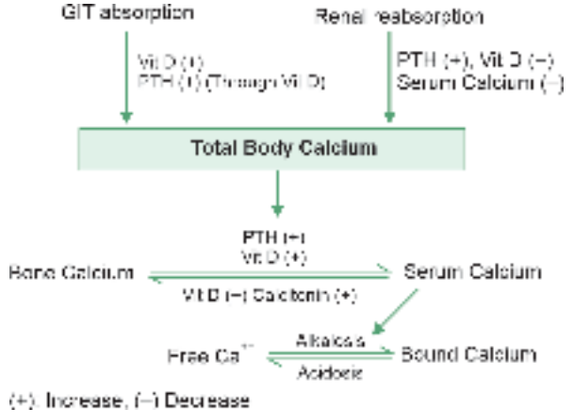

Fig. 7.2: Calcium regulation.

kidneys and mobilization from bones. PTH levels are controlled by a feedback mechanism, dependent on serum calcium levels.

- *Vitamin D* ($1,25(OH)_2D_3$) also increases gut absorption and renal reabsorption of calcium, *but* unlike PTH, facilitates its deposition in the bones rather than increasing serum levels.
- *Thyrocalcitonin hormone* from parafollicular cells of thyroid is antagonistic to PTH, decreasing bone resorption and increasing urinary calcium excretion.

Acid-base status predominantly affects ionic component without altering total serum levels. Ionic calcium levels are increased in acidosis due to movement of Ca^{++} out of the cell and decreased in alkalosis due to reverse movements. This *ionic component of plasma calcium is the prime determinant of its physiological activity*. As commonly measured serum levels include both the bound and ionic calcium, normal S. calcium levels do not exclude physiological hypo-/hypercalcemia. Ionic component may be normal despite low serum values, due to reduced bound fraction, e.g. in hypoproteinemia.

Hypocalcemia: Though the term 'hypocalcemia' is generally used to denote *S. calcium < 8.5 mg/dl* in children or <8 mg/dl in term newborns, clinical manifestations depend on ionic Ca^{++} levels (< 4.0 mg/dl).

If facility to measure ionic Ca^{++} is not available, it is worthwhile to measure S. albumin levels simultaneously. In normo-albuminic children, low S. calcium reflects ionic hypocalcaemia. However, in hypo-albuminic states, disproportionately low S. calcium levels should be demonstrated to identify ionic hypocalcaemia *(for each 1 gm/dl fall in S. albumin below 4 gm/dl, S. calcium levels fall by ~0.8 mg/dl)*.

Ionic Ca^{++} levels are also altered in acid–base imbalance, i.e. increased in acidosis and decreased in alkalosis (0.1 unit change in pH = 10% change in ionic calcium levels).

Causes: Hypocalcaemia is rarely dietary except in top-fed infants, where high phosphate content of formula feeds prevents adequate calcium absorption. Common causes of hypocalcaemia are listed in **Table 7.9**.

Clinically, latent or manifest *tetany* is the typical manifestation of symptomatic hypocalcaemia (discussed below), though generalized seizures are common in infancy. Less severe cases may present with irritability and cramps/twitching.

Management: Hypocalcaemic seizures *or* tetany is treated as follows:

- *Immediate* IV calcium gluconate 10% (2 ml/kg) infusion slowly over 8–10 minutes with cardiac monitoring for bradycardia or arrhythmia. IV site should be observed carefully during the injection as subcutaneous effusion may cause local necrosis.

TABLE 7.9: Causes of hypocalcemia

a. Vitamin D deficiency:
- Nutritional
- Malabsorption
- Chronic liver *or* renal disease

b. Decreased parathormone (PTH) activity:
- Hypoparathyroidism
- Pseudohypoparathyroidism

c. Hyperphosphatemia:
- Formula feeding
- Familial *or* chronic renal disease

d. Magnesium deficiency

e. Alkalosis *or* over-correction of acidosis

- *Immediate therapy should be followed by* IV calcium boluses as above repeated every 6–8 hours till next 24–48 hours. In mild cases, oral calcium supplementation (40–80 mg/kg/day) is enough, preferably with vitamin D.
- *In cases refractory to calcium boluses, concurrent* hypomagnesemia is likely and must be treated with IV magnesium sulphate 50% infusion as 25–50 mg/kg diluted 5–10 times in normal saline, which may be repeated every 6 hours, if required.
- Reduction of phosphate content in formula feeds may be necessary to reduce the risk of recurrence.

Tetany is a clinical entity, indicative of *neuronal hyperexcitability* due to abnormal concentration of various ions in the fluid bathing nerve cells.

Causes: Tetany is caused by:

- Hypocalcaemia (S. ionic Ca^{++} < 3.0 mg/dl)
- Hypomagnesemia (S. Mg^{++} < 1.0 mg/dl)
- Alkalosis: Respiratory *or* metabolic.

Clinical manifestations: *Carpopedal spasm* is the hallmark of tetany, though latent tetany is more common. Important signs of latent/manifest tetany are as follows:

- ***Latent tetany:***
  - *Chvostek sign*—facial twitching after tapping over the facial nerve at angle of mandible;
  - *Trousseau sign*—carpopedal spasm after squeezing of upper arm or during blood pressure measurement;
  - *Peroneal sign*—carpopedal spasm, after tapping over the peroneal nerve behind lateral malleolus;
  - *Erb's sign*—lower excitatory threshold on electrical stimulation of peripheral nerves;
  - Prolonged QTc interval (> 0.45 sec)
- ***Manifest tetany:***
  - *Carpopedal spasms,* i.e. flexion of wrists, extension of fingers, adduction of thumb with/without extension and adduction of feet **(Fig. 7.3)**;
  - *Laryngeal spasms* with stridor, croup or sudden death due to choking;
  - *Paresthesia,* i.e. tingling and numbness of fingers and toes;
  - *Generalized seizures* in infancy.

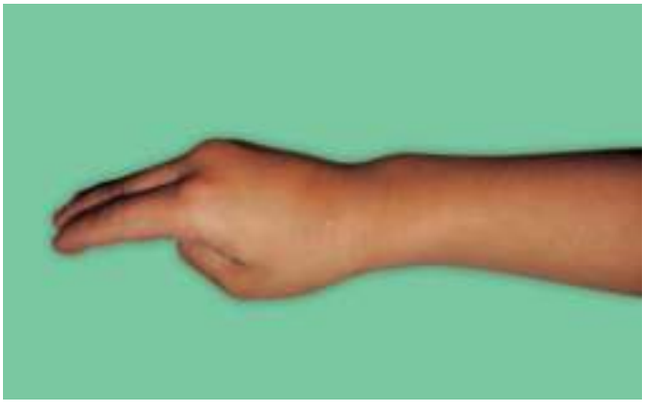

Fig. 7.3: Tetany—carpopedal spasm.

Treatment depends on the urgent correction of primary metabolic defect, e.g. hypocalcemia, hypomagnesemia or alkalosis. Careful re-breathing into an overhead bag to increase pCO_2 may control alkalotic tetany.

Hypercalcemia is relatively less common, defined as *S. calcium >11 mg/dl.*

Causes: Hypercalcemia is usually a chronic metabolic abnormality, secondary to *increased* parathyroid hormone or vitamin D activity or *low* phosphates to bind free calcium **(Table 7.10)**.

Clinically hypercalcemia presents with:

- Impaired urinary concentration, leading to polyuria and polydipsia;
- Hypercalciuria with nephrocalcinosis, tubulointerstitial nephropathy and nephrolithiasis;
- Lethargy, confusion, headache and coma in severe cases
- Arrhythmia, due to sudden hypercalcemia following IV calcium administration.

Treatment is indicated only when S. calcium levels cross 12 mg/dl and includes:

- Normal saline infusion along with diuretics, to increase calcium excretion in acute cases.
- Bisphosphonates, e.g. pamidronate or etidronate to block bone resorption and treat chronic hypercalcemia, e.g. in malignancies, immobilizations and hyperparathyroidism. IV calcitonin (4–8 U/kg q6hr) may also be used in some cases.
- Peritoneal dialysis in selected cases, specially in those with renal failure.
- Surgical intervention may be needed in cases with hyperparathyroidism with persistent hypercalcemia (> 12.5 mg/dl) and recurrent renal stones.

TABLE 7.10: Causes of hypercalcemia

- Primary hyperparthyroidism
- Hypervitaminosis D (Iatrogenic)
- *Bone demineralization:* Immobilization, malignancy
- Iatrogenic calcium overdose
- *Low phosphate intake:* LBW, milk-alkali syndrome
- *Increased phosphate excretion:* Thiazide diuretics
- *Others:* William syndrome*, thyrotoxicosis

*Elfin facies, hypercalcemia and supravalvular aortic stenosis.

7.5 MAGNESIUM DISORDERS

Magnesium is the second most important intracellular ion after potassium, responsible for maintenance of normal cellular enzyme activity for protein and fat metabolism as well as electric activity in nerves and muscles. *Normal serum magnesium levels are 1.5–1.8 mg/dl.*

RDA for magnesium varies from 30 mg in infants to ~200–400 mg in older children and adolescents.

Sources: Magnesium is present in plant chlorophyll, with green vegetables, e.g. legumes, nuts and whole grains as predominant source of dietary magnesium. Milk is a poor source.

Physiology: Since >99% of magnesium is intracellular, serum levels are unreliable indicators of magnesium status. Dietary intake usually exceeds normal requirements and physiological magnesium balance is mainly determined by its renal excretion from thick ascending loop of Henle and regulated by: (a) parathormone, (b) thyrocalcitonin, and (c) serum calcium levels. Parathormone enhances magnesium absorption from the gut and decreases excretion in the urine.

Hypomagnesemia: Although clinical severity may not correlate with serum levels, the term *hypomagnesemia* denotes S. magnesium levels <1.3 mg/dl.

Causes: Magnesium deficiency is rarely dietary except in cases of severe malnutrition or excessive consumption of junk foods (magnesium is eliminated during food processing). Secondary deficiency is common in malabsorption states and renal diseases **(Table 7.11)**.

Clinically hypomagnesemia induces skeletal resistance to parathormone, leading to hypocalcemia. Consequently, hypomagnesemia and hypocalcemia frequently co-exist and present with:

- *Neuromuscular irritability*, e.g. tetany, seizures and tremors, and
- *Cardiac* arrhythmia or ECG changes.

Severe hypomagnesemia may lead to mental changes, e.g. irritability and disorientation as well as respiratory paralysis. Hypokalemia and acidosis is also common in severe hypomagnesemia. Hypomagnesemia should always be suspected in a case of tetany, which does not respond to IV calcium therapy.

Treatment: Severe hypomagnesemia or hypomagnesemic tetany is treated with slow infusion of IV magnesium sulphate 50% as 25–50 mg/kg (2.5–5 mg/kg of elemental

TABLE 7.11: Causes of hypomagnesemia

a. Reduced absorption/intake
- Malabsorption syndrome
- Prolonged IV therapy (without magnesium)
- Protein-energy malnutrition

b. Increased urinary losses
- Hypoparathyroidism
- Renal tubular acidosis
- Nephrotoxic drugs
- Hyperaldosteronism
- Hypercalcemia

c. Familial hypomagnesemia

d. ***Others:*** Bartter syndrome, mitochondrial disorders

magnesium), diluted 5–10 times in normal saline, which may be repeated every 6 hours to the maximum of 200 mg/kg/day. Lower doses should be used in cases with renal disease. Concurrent hypocalcemia and hypokalemia also needs correction. Asymptomatic cases may be treated with oral magnesium supplements.

Hypermagnesemia is uncommon, sometimes seen in cases with chronic kidney disease or prolonged used of magnesium containing antacids. Symptoms are non-specific with nausea, vomiting and weakness in milder cases, though severe cases may develop altered sensorium, respiratory depression and arrhythmia.

Treatment involves removal of the source along with IV calcium therapy in severe cases to antagonize cardiac and neuromuscular effects of extracellular magnesium excess. Rarely, dialysis may be needed in very severe and symptomatic hypermagnesemia.

7.6 ACID–BASE DISORDERS

Normal acid–base regulation in body revolves around the concentration of hydrogen (proton) ions in body fluids, denoted as *pH*-the negative algorithm of free H^+ concentration.

Normal blood *pH* ranges between *7.35 and 7.45*. H^+ ions are continuously produced during various metabolic activities including dissociation of body *acids* (H^+ donor), e.g. H_2CO_3 and neutralized by body *bases* (H^+ acceptor), e.g. –OH, $–HCO_3$, NH_3, phosphates, etc.

Maintenance of normal blood pH depends on the rate of H^+ ion production and their neutralization. Excess production or deficient neutralization of H^+ ions lowers blood pH (*acidosis*), while reduced production or over-neutralization leads to increased pH (*alkalosis*).

Thus, actual blood pH depends on a ratio between its bases and acids, also depicted by *Henderson-Hasselbalch equation*, i.e.

$$pH = pK + \log \text{base/acid}$$

*pK is a constant, derived from dissociation of acid–base pair.

7.6.1 NORMAL ACID–BASE REGULATION

As H^+ ions are produced and eliminated at a variable rate, continuous regulation of normal acid–base balance depends on:
- Immediate *buffering mechanisms* to prevent rapid changes in pH, and
- Subsequent *compensatory mechanisms* to correct the actual biochemical change.

A. Buffering mechanisms: Immediately after production, H^+ ions are neutralized by certain body *buffers*, i.e. the substances that resist sudden pH changes by accepting or releasing extra H^+ ions.

The principal buffer in extracellular compartment (ECF) is *bicarbonate-carbonic acid system*, denoted by following bi-directional equation:

$$(H^+) + (HCO_3^-) \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2$$

The direction in which this equation runs, depends on the rate of H^+ production and their concentration in ECF. From the above equation it is obvious that:
- Rightward movement of this equation leads to excessive clearance of H^+ ions (*alkalosis*), while leftward movement leads to accumulation of H^+ ions (*acidosis*)
- Excess production of H^+ *or* depletion of HCO_3^- – due to any cause, leads to excess of H^+ ions in body (*metabolic acidosis*)
- Excess accumulation of HCO_3^- *or* depletion of H^+ due to any cause, leads to deficit of H^+ ions in body (*metabolic alkalosis*)
- Retention of CO_2 due to any cause drives this equation towards left, leading to inadequate buffering of H^+ ions (*respiratory acidosis*)
- Hyperventilation with CO_2 wash-out derives this equation to the right, leading to rapid clearance of H^+ ions (*respiratory alkalosis*)

Other important, though less efficient, buffer systems in body include, e.g. hemoglobin, proteins, phosphates, ammonia-ammonium buffer, etc.

B. Compensatory mechanisms: Abovementioned buffering mechanisms prevent rapid fluctuations in blood pH *but* do not correct the actual acid-base imbalance. Further, this neutralization leads to excess HCO_3^- utilization, disturbing normal CO_2/HCO_3^- ratio and limiting further buffering capacity.

Actual correction of acid–base imbalance after initial buffering is a slow process, which aims to normalize pCO_2/HCO_3^- ratio and eliminate excess H^+ ions by:
- *Pulmonary regulation*, i.e. increased/decreased excretion of CO_2, by changes in respiratory rate/depth;
- *Renal regulation* by:
  - increased/decreased reabsorption of HCO_3^- in proximal tubules and ascending loop of Henle,

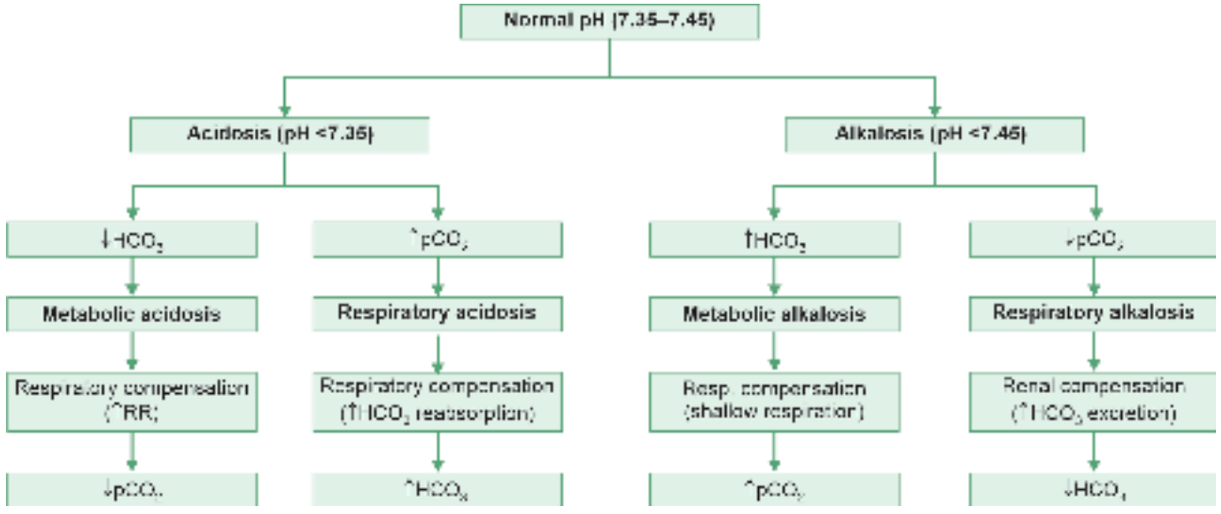

Fig. 7.4: Pathophysiology of simple acid–base disorders

– replacement of depleted HCO_3^- by production of new HCO_3^- in distal tubules and collecting ducts,
– actual H^+ excretion/secretion in distal tubules and collecting ducts.

In general, metabolic acidosis *or* alkalosis is compensated by pulmonary mechanisms, i.e. via increased or decreased CO_2 excretion respectively, while respiratory acidosis *or* alkalosis is compensated by renal mechanisms, i.e. increased or decreased HCO_3 excretion, respectively.

Thus, any acid–base imbalance is corrected by a two-step process:

a. changes due to initial buffering mechanism (*primary parameter*) during early stages, and
b. changes due to compensatory mechanism (*secondary parameter*) after some time.

As a thumb rule, in uncompensated pH disturbance, primary parameter is altered but secondary parameter is normal. On the other hand, in compensated state, primary as well as secondary parameter move in same direction. *For example*, in uncompensated metabolic acidosis, primary parameter (HCO_3) is reduced but pCO_2 is normal, while in compensated state, both HCO_3 and pCO_2 are reduced.

Figure 7.4 summarizes important buffering and compensatory mechanisms in various acid–base disturbances.

7.6.2 EVALUATION OF ACID–BASE STATUS

Clinical diagnosis of acid–base imbalance needs evaluation of *three* parameters on arterial blood gas (ABG) report-*pH, HCO_3 and pCO_2*. Normal range of these parameters are given in **Table 7.12**.

TABLE 7.12: Important acid–base parameters in ABG report

Parameter	*Normal range*
pH	7.35–7.45
pCO_2	35–45 mm Hg*
HCO_3	21–28 mEq/L

*Also denoted as torr units: 1 torr = 1 mm Hg.

Interpretation of an ABG report involves answers to following questions:

a. **Whether blood pH normal or abnormal?**

Normal blood pH varies from 7.35 to 7.45. Lower pH <7.35 indicates acidosis, while higher pH >7.45 indicates alkalosis. However, *normal pH does not exclude underlying acid–base imbalance*, as it could return to normal after some time due to compensatory mechanisms despite persistence of physiological abnormality.

b. **Whether pH abnormality is metabolic or respiratory in origin?**

Answer to this question requires study of two major pH determinants—HCO_3 or pCO_2, to identify primary altered parameter and direction of change. Predominant changes in HCO_3 values indicate either metabolic acidosis (↓ HCO_3) *or* metabolic alkalosis (↑ HCO_3). On the other hand, predominant changes in pCO_2 values indicate respiratory acidosis (↑ pCO_2) or respiratory alkalosis (↓ pCO_2). In later stages however, it may be difficult to identify primarily altered parameter due to compensatory change in other parameter. In such situations, clinical clues help to identify origin of pH abnormality.

c. **Whether any compensatory change has occurred?**

As the pH is a primarily a ratio between HCO_3 and pCO_2 (excluding effects of other buffers), compensatory mechanisms attempt to change the secondary parameter in the *same direction* as the primary abnormality, to restore normalcy. For example, ↓ HCO_3 in metabolic acidosis is compensated

by increased respiratory efforts to ↓ pCO_2; or ↑ pCO_2 in respiratory acidosis is compensated by excess renal bicarbonate reabsorption to ↑ HCO_3. Normal values of secondary parameter indicate absence of compensation, while altered values indicate partial or adequate compensation, discussed in next step.

d. **Whether compensation is adequate or inadequate?**

e. Efficacy of compensatory mechanisms depends on the time available for compensation and adequate pulmonary or renal functions. For example, metabolic acidosis may not be adequately compensated in a poorly ventilated child, who is unable to eliminate extra CO_2 for compensation. Compensation is considered as *adequate* if the secondary parameter has changed in following proportions to the change in primary parameter:
   - In metabolic acidosis, 1 mEq/L drop in HCO_3^- is compensated by 1.2 mm Hg drop in pCO_2.
   - In metabolic alkalosis, 1 mEq/L rise in HCO_3^- is compensated by 0.7 mm Hg rise in pCO_2.
   - In respiratory acidosis, 10 mm Hg rise in pCO_2 is compensated by 3.5 mEq/L rise in HCO_3^-.
   - In respiratory alkalosis, 10 mm Hg drop in pCO_2 is compensated by 5 mEq/L drop in HCO_3^-.

Proportionately lesser change in second parameter indicates inadequate compensation.

Following ***examples*** illustrate the interpretation of an ABG report:

- pH 7.25, pCO_2 58, HCO_3^- 25: Low pH indicates acidosis, high pCO_2 indicates respiratory acidosis and normal HCO_3 indicates *uncompensated respiratory acidosis*.
- pH 7.48, pCO_2 20, HCO_3^- 17: High pH indicates alkalosis, low pCO_2 indicates respiratory alkalosis and simultaneous reduction in HCO_3 indicates *compensated respiratory alkalosis*.
- *pH 7.2, pCO2 40, HCO3⁻ 18:* Low pH indicates acidosis, low HCO_3^- indicates metabolic acidosis and normal pCO_2 indicates *uncompensated metabolic acidosis*.
- *pH 7.5, pCO_2 39, HCO_3^- 30:* High pH indicates alkalosis, high HCO_3^- indicates metabolic alkalosis and normal pCO_2 indicates *uncompensated metabolic alkalosis*.

7.6.3 SPECIFIC ACID–BASE DISORDERS

Salient features of major acid–base abnormalities are as follows:

Metabolic acidosis: Primary abnormality in metabolic acidosis is decreased in HCO_3^- levels, either due to external losses or excess utilization to titrate H^+ ions during buffering process. During the compensatory phase, low HCO_3^- levels are compensated by increased elimination of CO_2 via respiratory route. Bicarbonate losses via kidney or gastrointestinal tract are also compensated by relative increase in chloride levels (hyperchloremia).

TABLE 7.13: Causes of metabolic acidosis

With normal anion gap (Hyperchloremic acidosis):
- Renal loss of HCO_3^-: Proximal RTA, renal failure
- GIT loss of HCO_3^-: Diarrhea
- ↓ H^+ excretion: RTA type I/IV, potassium sparing diuretics
- ↑ H^+ production: TPN, ammonium chloride poisoning

With high anion gap (Normochloremic acidosis)
- ↑ acid production/accumulation
  - *Lactic acidosis:* Sepsis, shock, hypoxia
  - *Ketoacidosis:* Diabetes ketoacidosis, starvation
  - *Others:* IEM, organic acidemia, salicylate poisoning
- Failure of acid excretion, e.g. renal failure
- Dilutional hypobicarbonatemia (HCO_3^- free fluid therapy)

RTA: Renal tubular acidosis; **TPN:** Total parenteral nutrition; **IEM:** Inborn errors of metabolism.

Etiology: Metabolic acidosis may be with: (a) *normal anion gap* due to loss of bicarbonates or accumulation of H ions or with, (b) *increased anion gap* due to accumulation of other acids, e.g. lactic acid or ketoacids, etc. *Relative HCO_3^- deficiency* due to bicarbonate-free fluid therapy (*dilutional hypobicarbonatemia*) may also lead to metabolic acidosis with normal anion gap **(Table 7.13)**.

Clinically, acute metabolic acidosis presents with signs of:

- Compensatory respiratory effort, e.g. *Kussmaul's breathing* – rapid and deep respiration, and
- Acidosis *per se* leading to peripheral vasodilatation and consequently hypotension, pulmonary edema and tissue hypoxia.

Chronic metabolic acidosis may be asymptomatic or present with anorexia, weight loss, vomiting and muscle weakness.

Diagnosis of *acute* metabolic acidosis is indicated by lower pH < 7.35, and low HCO_3^- levels, while *compensated* state is also associated with low pCO_2 levels. For full compensation, 1 mEq/L drop in HCO_3^- is compensated by 1.2 mm Hg drop in pCO_2.

Anion gap: Next step in etiological evaluation of metabolic acidosis is calculation of anion gap, i.e. the difference between total measurable cations and anions, i.e. *serum Na^+ and K^+ on one side and serum HCO_3^- and Cl^- on other side.* Normally, cationic side exceeds anionic side by ~12 mEq/L, due to a pool of non-titrable acids (*), as shown in following equation:

$$(\text{Serum})\ Na^+ + K^+ = HCO_3^- + Cl^- + (*)$$

Anion gap is increased (>16 mEq/L) in metabolic acidosis due to accumulation of non-titratable acid (with corresponding fall in measurable anions), e.g. in renal failure, lactic acidosis, diabetic ketoacidosis, salicylate poisoning, inborn errors of metabolism, etc.

Anion gap remains normal in metabolic acidosis due to bicarbonate losses with: (a) corresponding increase in Cl^- levels (hyperchloremic acidosis), e.g. renal tubular acidosis, hypoadrenal states, etc. or (b) corresponding drop in K^+ levels, e.g. diarrhea.

Management of metabolic acidosis mainly includes correction of underlying cause, though *alkali therapy* may be necessary in severe acidosis (pH <7 or HCO_3^- <5 mEq/L or salicylate poisoning) as follows:

- Calculate precise HCO_3 requirement by following formula:

  = (desired HCO_3 – actual HCO_3) × weight × 0.6*

  (*distribution coefficient for bicarbonates in body).
- Infusion only half of this amount as 7.5% $NaHCO_3$ over 3–4 hours (1 ml = 0.9 mEq/L) along with fluid correction for hypotension/shock.

IV bicarbonate correction should be done slowly, as rapid correction of acidosis may precipitate tetany due to intracellular movement of calcium. In addition, these cases should be treated for primary cause, along with IV fluids to manage hypotension and shock.

Metabolic alkalosis: Primary event in acute metabolic alkalosis is actual *or* relative (due to H^+ ion depletion) increase in HCO_3^- levels, which is partly compensated by respiratory depression to retain CO_2. However, this compensatory response is always inadequate, limited by increasing hypoxia.

Etiology: Metabolic alkalosis is mainly caused by: (a) excessive GIT losses of H^+ ions with chlorides, e.g. loss of gastric acids in vomiting, or (b) bicarbonate excess, due to exogenous administration *or* increased renal reabsorption **(Table 7.14)**. Infantile hypertrophic pyloric stenosis (IHPS) is an important cause of hypochloremic metabolic alkalosis.

Metabolic alkalosis is also classified as *Chloride-responsive* when caused by gastrointestinal losses of H^+ and Cl^- ions, and *chloride-resistant* when due to renal causes.

TABLE 7.14: Causes of metabolic alkalosis

Increased loss of H^+ ions (hypochloremic/Chloride-responsive)
- Persistent vomiting
- Prolonged nasogastric aspiration
- Infantile hypertrophic pyloric stenosis
- Others: Cystic fibrosis, chloride losing diarrhea
- Severe dehydration: Diuretics

Increased reabsorption of HCO_3 (chloride-resistant)
- Congenital adrenal hyperplasia*
- Cushing syndrome*
- Hyperaldosteronism*
- Renovascular diseases*
- *Others:* Bartter syndrome, Gitelman syndrome

Exogenous intake of bicarbonates
- IV/oral bicarbonate therapy
- Milk–alkali syndrome
- Large blood transfusions (citrate blood)

*With hypertension

Clinically, metabolic alkalosis presents with:

- S*hallow respiration* due to compensatory respiratory depression, and
- *Signs of hypocalcemia,* e.g. neuromuscular irritability, perioral paresthesia and alkalotic tetany, as alkalosis promotes calcium-binding with albumin, leading to ionic hypocalcemia.

Diagnosis of *acute* metabolic alkalosis is indicated by: (a) higher pH >7.45 and (b) elevated HCO_3^- levels, while *partially compensated* state is associated with some rise in pCO_2 levels. For full compensation, 0.7 mm Hg rise in pCO_2 is expected for each mEq/L rise in HCO_3 levels, though it is rarely achieved.

Urinary chloride levels may be used to differentiate between chloride-responsive (<10 mEq/L) and chloride-resistant (> 20 mEq/L).

Management depends on the primary cause. Chloride-responsive metabolic alkalosis may be corrected with replenishment of contracted ECF with normal saline and added potassium chloride to bring pH <7.55 and biocarbonate levels < 40 mEq/L.

Chloride-resistant metabolic alkalosis is difficult to treat and treatment includes: (a) acetazolamide therapy to promote urinary bicarbonate excretion, (b) cautious administration of IV hydrochloric acid (0.5 x weight x desired fall in plasma bicarbonates) or oral ammonium chloride supplementation, and (c) dialysis in severe cases.

Respiratory acidosis: Primary event in respiratory acidosis is *CO_2 retention* during acute phase ($PaCO_2$ >45 mm Hg), subsequently compensated by increased tubular reabsorption of bicarbonates as well as increased excretion of H^+ ions (as ammonium and titratable acids). Some cases may have coexistent metabolic acidosis, due to secondary effects of hypoxia and consequent lactic acidosis.

Etiology: Respiratory acidosis is usually caused by *inadequate CO_2 excretion* due to poor alveolar ventilation or rarely due to increased CO_2 production, e.g. high fever or extensive burns **(Table 7.15)**.

Clinically, these cases present with:

- Signs of respiratory distress due to primary cause, and
- Signs of hypercapnia (*CO_2 narcosis*), e.g. headache, vomiting and altered sensorium, due to consequent cerebral vasodilatation and raised intracranial pressure.

Diagnosis of *acute* respiratory acidosis is indicated by lower pH <7.35, and elevated pCO_2, while *compensated* state is associated with rise in plasma HCO_3^- levels. While compensation begins in 6–12 hours, full compensation may take 3–5 days and needs HCO_3^- levels to rise by 3.5 mEq/L for each 10 mm Hg rise in pCO_2.

TABLE 7.15: Cause of respiratory acidosis

Loss of central respiratory drive
- CNS infections, tumors, etc.
- Drugs, e.g. narcotics, alcohol

Weakness of respiratory musculature
- Chronic neuromuscular disorders
- Acute respiratory muscle paralysis

Pulmonary diseases
- Restrictive lung diseases, e.g. severe scoliosis
- Extensive lung/airway disease

Miscellaneous (Increased CO_2 production)
- High fever or extensive burns

Management includes adequate ventilation/perfusion for treatment of primary cause and ventilator assistance, if necessary. *Alkali therapy should never be used till adequate ventilation* is established as it will worsen CO_2 retention ($HCO_3^- + H^+ > H_2CO_3 > H_2O + CO_2$) and may produce hyperosmolality and cardiac failure.

Respiratory alkalosis: Primary change in the respiratory alkalosis is *decreased pCO_2*, subsequently compensated by decreased tubular absorption of bicarbonates.

Etiology: Respiratory alkalosis is caused by *excessive CO_2 wash-out*, due to hyperventilation, e.g. psychogenic causes, high fever, mechanical overventilation or early salicylate poisoning.

Clinically, these cases present with:
- Hyperventilation due to primary cause, and
- Signs of hypocalcemia, e.g. neuromuscular irritability, peri-oral paresthesia and alkalotic tetany, as alkalosis promotes calcium-binding with albumin, leading to ionic hypocalcemia.

Diagnosis of *acute* respiratory alkalosis is indicated by higher pH >7.45, and reduced pCO_2, while *compensated* state is associated with drop in HCO_3^- levels. Full renal compensation is rarely achieved and requires ~5 mEq/L drop in HCO_3^- for each 10 mm Hg drop in pCO_2.

Management depends on primary cause and correction of ventilatory settings. Acidifying agents, e.g. ammonium chloride are not indicated.

7.7 PARENTERAL FLUID THERAPY

Parenteral fluid therapy is the essential component of critical child care, required not only to correct dehydration but also to provide maintenance fluid/electrolyte requirements in children who cannot be given oral fluids due to critical sickness, surgery, persistent vomiting or any other reason.

7.7.1 PRINCIPLES OF FLUID THERAPY

Some general principles for parenteral fluid therapy are as follows, while therapy in specific circumstances is discussed later.

Indications: Parenteral fluid therapy is mainly indicated in children with:
- Severe dehydration, hypotension or shock, when immediate volume replacement is life-saving,
- Persistent vomiting, with poor tolerance to oral feeds.
- Critical illnesses, e.g. coma, seizures, respiratory distress, etc. when oral feeding is not possible or contraindicated.
- Pre-and post-surgery fluid therapy.
- Systemic disorders, e.g. renal failure or CCF, which require fine-tuning of fluid and electrolyte intake.

Routes: Parenteral fluid therapy requires secure IV access with a peripheral venous line. In emergency, intraosseous infusion may be used temporarily for rapid fluid correction till IV access is secured (Ch 32.3).

Fluid volume requirements of each child vary according to their age, body weight, presence/severity of dehydration and primary disease, though approximate requirements may be calculated as ***sum-total*** of following:
- ***Maintenance requirements,*** essential for basal metabolism as well as to replenish normal fluid losses via urine, stools and insensible means, e.g. lungs and skin. Though dependent on metabolic rate (1 ml water for each caloric expenditure), maintenance fluid and electrolyte requirements may be practically calculated by actual body weight as per *holiday and segar* formula **(Table 7.16)**. In smaller children (6–15 kg) maintenance volume must preferably be calculated with body surface area as 1400–1500 ml/m^2.

  Calculated fluid requirements must be *increased* by 20–30% in conditions with higher insensible losses, e.g. fever, hyperventilation, warmer care, etc.; and *decreased* by 20–30% in cases with oliguria or less insensible losses, e.g. hypothermia.
- ***Deficit requirements*** depend on the severity and type of dehydration (iso-/hypo-/hyper-natremic), though generally calculated as 10 ml/kg for each percent of expected weight loss due to dehydration, i.e. ~5%, 10% and 15% for mild/moderate/severe dehydration in infants and ~3%, 6% and 9% respectively in older children.

  For example, if a 4 years child weighs 15 kg and has moderate dehydration, his/her weight loss is expected to be 6% and fluid deficit is expected to be 15 × 6 × 10 = 900 ml. **Table 7.16** gives fluid and electrolyte requirements in dehydration of variable severity. Electrolyte requirements have been calculated assuming 60:40 fluid loss from ECF and ICF, as common in isotonic dehydration.
- ***Concomitant fluid and electrolyte losses*** in stools, gastric aspirate, etc. need periodic assessment

TABLE 7.16: Fluid requirements in normal children

A. For maintenance:
Water:
(BW<10 kg) : 100 ml/kg
(BW 10–20 kg) : 1000 ml + 50 ml/kg for wt >10 kg
(BW>20 kg) : 1500 ml + 20 ml/kg for wt >20 kg (max 2400 ml)

B. For deficit:
Water (10 ml/kg of expected wt loss* due to dehydration)
Mild dehydration : 30 ml/kg (50 ml/kg in infants)
Moderate dehydration : 60 ml/kg (100 ml/kg in infants)
Severe dehydration : 90 ml/kg (150 ml/kg in infants)

C. Concomitant losses

*Expected wt loss is ~ 3% in mild, ~6% in moderate and ~9% in severe dehydration; (higher—~ 5%, 10%, 15%, in infants).

TABLE 7.17: Composition of external abnormal fluid losses

Fluid loss	*Sodium (mEq/L)*	*Potassium (mEq/L)*	*Chloride (mEq/L)*
Diarrheal stools	60	25	15
Vomiting/gastric aspirate	60	10	90
Ileostomy loss	130	10	115
Burns*	140	5	110

* and 3–5 gm/dl of protein

and replacement with suitable fluids. Electrolyte requirements for this replacement depend on composition of body fluid/s, which are being lost **(Table 7.17)**. About 10 ml/kg is considered as the concurrent loss for each large watery stool, and ~2 ml/kg for each vomiting.

Choice of parenteral fluids depends on the estimated electrolyte requirements, need for nutrition (dextrose *vs* non-dextrose fluids) and primary disease. Various IV fluids with different electrolyte/dextrose concentrations are available commercially *or* can be prepared in hospital pharmacy under strict aseptic precautions **(Table 7.18)**.

- *For maintenance therapy*, isotonic fluids, e.g. normal saline in DW 5% are recommended at present in all children except in neonates <28 days or those with cardiac/liver/renal disease, burns, malignancies or undergoing neurosurgery.

  Earlier recommendations of maintenance fluid therapy with hypotonic N/2 or N/5 saline in Dextrose 5% are no longer valid due to risk of hyponatremia.
- *For deficit correction,* choice of fluid varies according to the route of fluid-loss, e.g. stools, gastric aspirate, etc. *and* laboratory electrolyte values. In general, *Ringer lactate (Na^+ 131 mEq/L)* is preferred for this purpose in usual cases of diarrhea induced dehydration, with additional advantage of containing lactate that is converted into bicarbonate and prevents metabolic acidosis.

Monitoring: All cases on IV fluids should be monitored for changing needs of fluids/electrolytes, possibility of switch over to oral rehydration therapy and complications, e.g. overhydration, electrolyte disturbances, infection, thrombophlebitis or local extravasation.

TABLE 7.18: Electrolytes in common IV fluids

	Na^+	*K^+*	*Cl^-*	*Glucose*
Dextrose 5% (D5)	–	–	–	50
Dextrose 10% (D10)	–	–	–	100
Normal saline (NS)	154	–	154	–
Dextrose saline (DS)	154	–	154	50
N/2 saline in D5	77	–	77	50
N/5 saline in D5	30	–	30	40
Ringer lactate*	131	5	111	50
Isolyte P	25	20	22	50

Na, K and Cl values in mEq/L, glucose in gm/L
*also contains lactate 29 mEq, which is *in vivo* metabolized into bicarbonate to prevent acidosis

7.7.2 FLUID THERAPY IN CLINICAL PRACTICE

Fluid therapy in children requires precise calculations of fluid/electrolyte requirements, as the volume, composition and rate of administration for parenteral fluids varies with indication, circulatory status and laboratory values of electrolytes. Important determinants for initial fluid therapy include:

- Whether patient is dehydrated *or* requires only maintenance therapy?
- If dehydrated, what is its severity and type?
- What is the source of fluid loss?
- Whether and which electrolyte abnormalities are present?
- What is the state of renal and cardiac functions?

Standard fluid therapy is based on the type and severity of the dehydration as follows:

Isonatremic dehydration, the commonest type of dehydration, is characterized by fluid loss from both ECF and ICF in a ratio of ~60:40. More acute is the dehydration, greater is the proportion of ECF losses.

Parenteral fluid therapy in these cases aims for: (a) rapid correction of ECF-deficit and restoration of plasma volume in first few hours followed by, (b) slower correction of remaining deficit *plus* infusion of maintenance and concomitantly lost fluids, till oral rehydration (ORS) is possible. Though different protocols are followed in different institutions, a simple one is as follows:

Step I. Infuse 20 ml/kg of *Ringer lactate* or *normal saline* as bolus over 20 minutes to restore the intravascular volume, which may be repeated in cases of severe dehydration or shock. However, maximum rate of infusion should never exceed 30 ml/kg/hr to avoid volume overload. *Potassium is usually withheld in this*

phase. By the end of this phase, child is expected to be circulatory stable.

Step II. Calculate 24-hour fluid requirements as s*um total of maintenance + deficit needs*, as discussed earlier.

Step III. Subtract the volume already infused in step I from this 24-hr fluid requirement calculated in step II and infuse remaining volume over next 24 hours using Isotonic saline in DW 5%. Add 20 mEq/L of potassium in IV fluids after the urine output is established. In moderate to severe dehydration with fluid losses exceeding 5%, remaining volume should be infused more slowly over 48–72 hours, if switch-over to ORS is not possible.

Concomitant losses via stools, vomitus or gastric aspirate, etc. must be added to the calculated volume. IV $NaHCO_3$ (2–3 mEq/kg) may be added, if acidosis is suspected clinically but biochemical estimation is not possible.

Step IV. Gradual switch over to ORS, as soon oral feeds are acceptable.

Table 7.19 provides a representative example for calculation of fluid requirements in a one-year old child, weighing 10 kg with severe isotonic dehydration.

Hyponatremic dehydration: While ECF losses are relatively higher in hyponatremic dehydration due to fluid movements from ECF to ICF, fluid therapy is similar to that for isotonic dehydration, *except* that calculated sodium deficit should be gradually corrected over first 12–24 hours, using high-sodium IV fluids, e.g. Ringer lactate or N/2 dextrose saline. S*erum sodium correction should never exceed 10 mEq/L/24 hours.* Only *symptomatic* hyponatremia with seizures is treated with 3% NaCl infusion at the rate of 1–2 ml/min (max 12 ml/kg) till seizures are controlled.

Hypernatremic dehydration: As ECF losses are comparatively less in hypernatremic dehydration due to osmotic withdrawal of fluids from ICF, only 3/4th fluid correction is required in these cases, using low-sodium fluids, (e.g. N/2 dextrose saline). Sodium-free fluids should never be used in these cases due to risk of rapid drop in ECF sodium, osmotic fluid movement from ECF to ICF and cerebral edema. In any case, s*erum sodium fall should not exceed 8–12 mEq/L/24 hours.*

TABLE 7.19: Correction of severe dehydration in 10 kg child

Assumptions:
- Age: 1 year; weight: 10 kg
- Severe dehydration
- Isotonic dehydration

Total fluid requirements:
For maintenance : 100 x 10 = 1000 ml +
For deficit : 150 x 10 = 1500 ml
Total 24 hour : 2500 ml

Schedule of infusion:
- IV bolus (20 min) : 200 ml[1] as Ringer lactate/NS, no potassium
- Remaining fluids : 2500–200 ml = 2300 ml
- Next 24–48 hrs (slow IV)* : 2300 ml as NS with DW 5%, with potassium 20 mEq/L
- Add concomitant losses in later half of infusion

[1] 20 ml/kg * Switchover to ORS as soon as possible.

7.7.3 FLUID THERAPY IN SPECIFIC SITUATIONS

General guidelines for fluid therapy in specific situations are discussed as follows:

Fluid therapy in diarrhea may be considered as prototype of fluid and electrolyte therapy in pediatric practice, as diarrhea is the commonest cause of dehydration in children. Two methods of fluid therapy in diarrhea are in vogue—*Standard fluid therapy,* discussed earlier, and *rapid rehydration method*-later being more simple, practical and adequate in most cases.

Traditional fluid therapy in diarrhea, requires complex calculation, which is neither practical nor necessary in most cases as: (a) prompt restoration of ECF will itself facilitate physiological corrective mechanisms, and (b) most cases tolerate ORS soon after initial correction and do not need prolonged IV therapy.

At the peripheral community level with limited resources, recent studies have proved safety and efficacy of simpler *rapid rehydration* in moderate to severe dehydration (WHO plan C, Ch 14.10).

This strategy involves a *rapid infusion of Ringer lactate 30 ml/kg during first 30 min (1 hour in infants), followed by N/5 Dextrose saline ~ 70 ml/kg in next 2½ hours (5 hours in infants) and switch over to ORS, as soon as possible.*

Fluid therapy in gastric losses: Loss of gastric juices is the major cause of dehydration in cases with persistent vomiting, e.g. congenital hypertrophic pyloric stenosis *or in* children requiring continuous nasogastric aspiration, e.g. intestinal obstruction. As gastric fluid contains relatively less sodium and more chlorides and potassium, *hypokalemia and hypochloremic alkalosis* are most important electrolyte disturbances in these cases. Fluid therapy in them is similar to traditional fluid therapy, except that:
- N/2 dextrose saline may be preferred for deficit correction in these cases.
- Potassium replacement should begin as soon as the child has passed urine.
- Hypochloremic alkalosis may be corrected by high-chloride IV fluids, e.g. isolyte G; or NH_4Cl supplements after correction of hypokalemia.

Fluid therapy in critically sick children: Children with critical illnesses, e.g. acute neurological disorders (meningoencephalitis, head injury, hypoxic-ischemic injury, etc.), acute pulmonary disorders (pneumonia, asthma, respiratory failure) or those on ventilators, are likely to have fluid retention due to SIADH. A simple and reliable indicator of this problem is the presence of hyponatremia despite concentrated urine with urinary

sodium exceeding > 20 mEq/L. Important aspects of fluid therapy in these cases after initial fluid/electrolyte corrections, include:

- *Restriction of maintenance fluid* volume to 2/3rd of calculated requirements; and
- *Correction of hyponatremia*: No correction is necessary for asymptomatic hyponatremia as fluid restriction itself allows a gradual recovery of serum sodium levels. However, cases with symptomatic or severe hyponatremia require slow correction with relatively hypertonic fluids, e.g. Ringer lactate, along with a diuretic, e.g. furosemide to enhance free water excretion. Rapid correction with 3% NaCl infusion (1 ml/min to max 12 ml/kg) is indicated only in cases with hyponatremic seizures.

Fluid therapy in surgery: Most common error during peri-operative fluid therapy is the overhydration, specially with plain dextrose fluids without electrolytes.

- ***Pre-operative fluid therapy*** in children for elective surgery aims to provide adequate carbohydrates for sustenance and maintenance requirements of fluids and electrolytes, which may be met with *N/5 saline in dextrose 10%*. However, children for emergency surgery need pre-operative fluid and electrolyte correction according to primary disease and laboratory investigations.
- ***During surgery***, maintenance requirements should be given as isotonic normal saline *or* dextrose saline (without potassium), while surgical losses may be replaced with blood or plasma. As hyperkalemia is common during or immediately after surgery due to release of intracellular potassium after tissue trauma, potassium supplements should be avoided in this period.
- ***Post-operatively***, SIADH is common and maintenance fluids should be restricted to 2/3rd of usual requirements during first 24 hours. Ringer lactate is the preferred fluid during this period. Potassium supplementation is indicated only after first 24 hours, unless warranted by laboratory reports.

Fluid therapy in malignancy: These cases, specially those beginning with induction therapy, are at risk of tumor-lysis syndrome with hyperkalemia, hyperphosphatemia, hypocalcemia and hyperuricemia. Fluid therapy in these children should include additional maintenance fluids (usually 2–2.5 times) to ensure a urine output of 4ml/kg/hour, using *potassium-free fluids*.

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CHAPTER

8

Immunological Disorders

Mukesh Agrawal

Initial host-defense mechanisms against invasion by a pathogen include: (a) *anatomical* skin and mucosal integrity, (b) *physiological* milieu of the tissues, e.g. acidic gastric pH, (c) *mechanical* clearance of cell debris, e.g. mucociliary movements, and (d) *normal microbial colonizing flora* that competitively oppose invading pathogens. Once these barriers are breached, second line of defense is presented by *immunological system*, which is a complex interplay of various components, acting in unison to eliminate the invading pathogen *or* even an aberrant host-antigen, e.g. tumor cells.

8.1 BASIC CONSIDERATIONS

The hallmark of immune defense is recognition of a foreign or non-self antigen, as well as tolerance of own tissue antigen or self-antigen. Some basic concepts in immunology are as follows:

Antigen: The term *antigen* refers to a molecule recognizable by immunological cells, which have specific binding sites (receptors) for these molecules. Only a small portion of antigen (*epitope*), e.g. cell-wall component or DNA-nucleotide sequence, etc. is recognized by antigen-specific receptors, though complex antigens have many such epitopes. All antigens are not equally immunogenic. Proteins antigens are more immunogenic than carbohydrates, e.g. lipopolysaccharides (*haptens*). However, immunogenicity of haptens may be enhanced by conjugating them with protein vehicles, e.g. tetanus toxoid, as done in conjugate vaccines.

All cells have antigens, including viruses, bacteria, etc. and even the host's own cells. However, tolerance to self-antigens develops during early fetal life by selective elimination of those T-cells (*apoptosis*), which do not recognize self-antigens, i.e. major histocompatibility complex (MHC) antigens.

Major histocompatibility complex (MHC) is the surface antigen (glycoprotein), present on most human cells, including leukocytes (*human leukocyte antigen* or HLA). These antigens may be broadly divided into two types: *MHC class I molecules* (HLA-A, B, C) present on most the nucleated body cells and platelets; and *MHC class II molecules* (HLA-DP, DQ, DR), present on macrophages, dendritic cells and B cells.

HLA type of a person is determined by a cluster of genetic loci on short arm of 6th chromosome and denoted as HLA-B27, HLA-D8, etc. Major significance of HLA antigens lies in: (a) tissue typing before transplants to select suitable donor, and (b) their association with many autoimmune disorders.

Types of immunity: Immune-defense mechanisms may be broadly divided into:

- ***Innate immunity***, which is *antigen non-specific* and attempts to eliminate any invading pathogens before the development of antigen-specific adaptive immunity. It is provided by: (a) physical, chemical and mechanical barriers, (b) inflammatory response to bring *cellular elements* at the site of invasion, e.g. phagocytes and natural killer cells, to engulf and kill invading organisms, and (c) release of *chemical mediators,* e.g. cytokines and chemokines.

  Innate immune system also triggers development of adaptive immunity by processing the pathogen by *antigen-presenting cells,* i.e. macrophages and dendritic cells, and transport them to T-lymphocytes, largely present in lymph nodes.
- ***Adaptive (Acquired) immunity*** is *antigen-specific*, develops over few days/weeks after the first exposure and persists throughout the life due to development of memory B-cells, though not necessarily in protective range. Mediated by T cells ***(cell-mediated immunity)*** and/or B cell generated immunoglobulins ***(humoral immunity)*** adaptive immunity is responsible for clearance of primary infection and prevention of disease during subsequent exposures. Adaptive immunity may be induced by natural exposure (infection) or artificial exposure (vaccine).

Components of Immune System

As stated earlier, immunological mechanisms are mediated by various cellular and humoral components of immune system, as follows:

- *Antigen non-specific* components, e.g. phagocytes, dendritic cells, natural killer cells, complements, etc.
- *Antigen-specific* components, e.g. T-cells and B-cells (immunoglobulins).

There is considerable interdependence between these immunological mediators, which act in coordinated manner to induce adequate immune response.

I. Phagocytic system is the first line of immunological defense to: (a) engulf and digest foreign antigens, and (b) process them for presentation to antigen-specific cells.

It is mediated by two different cell types: (i) *circulatory phagocytes,* i.e. neutrophils and (ii) *tissue phagocytes,* i.e. macrophages, which are derived from monocytes and populate tissues like lung, liver, kidney, spleen, brain and lymph nodes. Neutrophilic phagocytes mainly act against pyogenic bacteria, while macrophages are predominantly involved in killing of intracellular organisms, e.g. mycobacteria, toxoplasma, etc. and inducing T-cell mediated immune response.

Phagocytosis of a foreign element involves a cascade of activity, including: (a) *recognition* of the invader as a non-self-antigen, (b) *chemotaxis*, i.e. recruitment of more phagocytic cells, mobilized from other sites as well as bone marrow, (c) *phagocytosis*, i.e. attachment and entrapment of antigen within phagocytes by a process of vacuolization, and (d) *microbiocidal activity* within the phagocytes to eliminate entrapped pathogens by various oxidative, hydrolytic or *defensins* mediated systems.

Phagocytosis is facilitated by: (a) specific antibodies on phagocytes, which act as *ligands* to bind them with pathogen, and (b) *opsonins* in serum-products of complement system, which neutralize anti-phagocytic factors on bacterial cells.

II. Dendritic cells are *antigen-presenting cells* widely distributed in skin, lungs and other tissues, which primarily act against *extracellular antigen*, e.g. microbial cell-wall components, dead host-cells, etc. These cells recognize a foreign antigen, collect a sample by endocytosis to process it into smaller peptide fragments and then migrate to regional lymph nodes to present them to T and B cells. Thus, these cells may be considered as *antigen-priming cells* for induction of acquired immunity.

III. Natural killer (NK) cells are lymphocytes *without T-cell receptors*, which primarily act against *intracellular antigens*, e.g. virus-infected cells and malignant cells, i.e. aberrant host cells and killing them. Recognition of intracellular antigen by these cells depends on: (a) antibody-coating on virus-infected cells, and (b) suppression of MHC molecules on aberrant/malignant host cells to render them as foreign antigens. Intracellular killing by NK cells is a complex process involving injection of target cells with cytotoxic granzymes.

IV. Complement system consists of many non-specific, heat-labile interacting protein components, which contribute to ~10% of total plasma globulin fraction.

These components are numbered (C_1, C_2 …, etc.) in order of the discovery and not in sequence of their activation. Complements and their by-products act as a principle mediator of inflammatory response, after nonspecific *or* specific antigenic challenge. Various components of complement system are activated in sequentially by two different pathways:

a. ***Classic pathway,*** which is primarily stimulated by immunological mechanisms, i.e. fixation of C_1 to Fc portion of antibody (antigen-specific) or C-reactive proteins (antigen-non-specific).
b. ***Alternative or properdin pathway,*** which is mainly stimulated by non-immunological stimuli, e.g. endotoxins, leukocyte degradation products, etc. *Or* after activation of a component of the classic pathway C_{3b}.

Both pathways converge at the level of C_3 activation, followed by a common sequence to generate highly active complement components, e.g. opsonins (C_{3b}), chemotactic factors (C_{5a}), mast-cell activators, i.e. anaphylatoxins (C_{3a}, C_{5a}), cell lysis activity (membrane attack complex). C_3 is most abundant and crucial component of complement system.

Complement system plays a vital role in both innate and adaptive immunity with: (a) neutralization of viruses, (b) opsonization of bacteria, (c) deactivation of endotoxins, (d) lysis of virus-infected or malignant cells, and (e) regulation of immune response by induction of granulocytosis or suppression of excessive antibody response.

Controlling mechanisms to prevent excess consumption of complement activity involve simultaneous activation of various complement inhibitors during complement cascade, e.g. C_1 inhibitor and others.

V. Cytokines *or* chemokines are glycoproteins, synthesized and released by immunologically activated lymphocytes (lymphokines), macrophages, monocytes and vascular endothelium.

Cytokines predominantly act as *immune messengers* to regulate immune response, i.e. to localize, limit or facilitate it, depending on the type of cytokines produced. Important cytokines are: *Interleukins* ($IL_{1–18}$), *interferons* (IFN-β, γ), *tumor necrosis factors* (TNF-α), *colony stimulating factors* (GM-CSF, G-CSF, M-CSF) and *erythropoietin*, etc.

Cytokines also participate in regulation of hematopoiesis and inflammation. Most of the cytokines act as both—facilitator *or* inhibitor of immune response, depending on the target cells.

VI. Acute phase proteins may be: (a) *pro-inflammatory*, e.g. C-reactive protein, which assists in recognition of pathogen/damaged cell, complement activation and cytokine production, or (b) *anti-inflammatory*, e.g. proteinase inhibitors or coagulation proteins, which help in wound healing.

VII. T lymphocytes may be considered as the *orchestra director* of acquired immunity, which not only mediate cellular immunity but also activate B-cell for immunoglobulin production.

Cell-mediated immunity (CMI) is mainly involved in: (a) immunity against intracellular organisms (viruses, mycobacteria), fungi and protozoa, (b) immune surveillance of cancer cells, and (c) graft-rejection or graft *versus* host disease.

T lymphocytes develop from stem cells in bone marrow, but migrate and mature in thymus. Thymic maturation involves three important changes: (a) *cluster differentiation*, i.e. switch-on of various surface markers-termed CD markers; (b) *positive selection*, i.e. development of T cells which recognize self-MHC antigens, and (c) *negative selection*, i.e. elimination of T cells which do not recognize self-antigens and may be self-destructive. Subsequently, these cells enter circulation and re-populate lymphoid organs, e.g. lymph nodes, spleen and Peyer's patches. Depending on their functions and CD markers, T cells may be divided into 2 major groups:

- ***T helper-inducer cells*** (CD_4 cells), which induce antibody production by B cells and regulate immune response by cytokines production. These cells are further divided into: *Th1 cells,* which are important for macrophage activation and cell-mediated immunity; and *Th2 cells,* which help in activation and differentiation of B cells and down-regulation of immune response. Th1 cells predominantly help in elimination of intracellular pathogens, e.g. viruses, while Th2 cells are more important for elimination of extracellular pathogens, e.g. helminths. *Excess Th1 or Th2 activity is a major contributing factor for autoimmunity and allergy, respectively.*
- ***Cytotoxic-suppressor cells*** (CD_8 cells), which are responsible for killing of virus-infected cells *or* tumor cells, as well as suppression of immune response.

VIII. B-lymphocytes are mediators of acquired humoral immunity, by production of antigen-specific or non-specific *immunoglobulins*.

Like T-cells, B-cells also develop from stem-cells in bone marrow. However unlike them, human B-cells mature in bone marrow itself (bursa of fabricius in birds), before circulating and populating lymphoid follicles in spleen, liver, tonsils and Peyer's patches. B-cells comprise 5–15% of total circulating lymphocytes. On antigenic stimulus, these cells differentiate into *plasma cells*, to produce various immunoglobulins.

B-cells are of two types: B_1 (CD_5) cells, which produce non-specific IgM immunoglobulins against variety of antigens; and B_2 cells which produce specific IgM, IgE and IgA antibodies in response to specific antigenic challenge.

IX. Immunoglobulins (Ig) or antibodies are serum proteins, produced by B-cells, which: (a) inactivate, agglutinate or opsonise antigens for phagocytosis, and (b) activate complement system for cytolysis. These immunoglobulins are present on the surface of B-cells (*surface immunoglobulins*) or secreted in extracellular medium (*secretory immunoglobulins*). Depending on their properties and role in immune system, immunoglobulins may be divided into 5 types:

- ***IgM*** constitutes ~10% of serum immunoglobulins and mainly remains within the circulatory compartment. IgM antibodies are the first class of immunoglobulins secreted after antigenic challenge, though levels decline soon after the infection is controlled within 2–3 months. Thus, *raised IgM levels indicate acute infection. IgM does not cross the placenta and high IgM levels in newborn indicate true fetal infection.*
- ***IgG,*** most abundant serum immunoglobulin (~70%), is produced later than IgM after primary antigenic exposure and persist longer for many months or years but in declining titers. Thus, *IgG levels may be high due to past infection and not necessarily indicate acute infection.* However, on a subsequent challenge with same antigen, IgG response is anamnestic, profound and persistent.

While predominantly present in serum, IgG diffuse well in tissues as well as *cross the placenta t*o transfer the maternal immunity to baby. Hence, *raised IgG titers in fetus or newborn may be due to maternal transmission and not necessarily indicate fetal infection.*

Four major subclasses of IgG are IgG_1, IgG_2, IgG_3 and IgG_{4C}. Of these, IgG_2 is unique, as it also responds to polysaccharide antigens.

- ***IgA*** contributes to ~15–20% of serum immunoglobulins (*serum IgA*), as well as also present in various body secretions (*secretory IgA*), e.g. nasobronchial or gut secretions, saliva, lacrimal fluid and colostrums (protective antibody in human milk).

  Secretory IgA is predominantly responsible for *local immunity*, i.e. clearance of antigen from mucosal sites. IgA does not activate complement system or provoke inflammatory response.
- ***IgE*** is present in miniscule amounts in serum but acts as principal mediator of immediate hypersensitivity (allergy) as well as also has some role in immunity against helminths.

  Two types of IgE antibodies are – *non-specific IgE*, present in serum/tissues of normal individuals which appear to defend against parasitic invasion; and specific or *reaginic* antibodies, synthesized on exposure to a specific allergen.
- ***IgD*** accounts for <1% of serum immunoglobulins with indefinite role, probably as an antigen receptor site on circulating B-cells.

Physiology of Adaptive Immune Response

Immune responses are initiated by the exposure to an antigen that carries a *danger signal*, e.g. bacterial products, endotoxin, viral DNA *or* tissue necrosis. Important steps in development of immune responses **(Fig. 8.1)** are as follows:

- **Innate immunity** directly attempts to eliminate invading pathogen by itself using: (a) physical, chemical and mechanical barriers, (b) inflammatory response to bring cellular elements, e.g. phagocytes and natural killer cells at the site of invasion to engulf and kill invading organisms as well as macrophages and dendritic cells (antigen-processing cells) to process the antigen/s of pathogens, and (c) release of chemical mediators, e.g. cytokines and chemokines.
- ***Antigen-processing***: Innate immunity also triggers development of adaptive immunity using these *antigen presenting cells,* to process the pathogens and express their antigen/s on the surface for recognition by immune cells. Processed antigens are transported to T lymphocytes, largely present in lymph nodes.
- **T-cell dependent response** is triggered by processed antigens and induce: (a) direct killing of virus-infected or tumor cells by cytotoxic or NK cells, (b) further activation of macrophages and cytotoxic cells by Th_1 cells, (c) differentiation of antigen-specific B-cells by T-helper or Th_2 cells, and (d) secretion of various cytokines, which act as immune messenger or regulator.

  Activate T-helper cells also stimulate B-cell differentiation to develop as plasma cells and produce specific immunoglobulins and memory B cells. Memory cells directly recognize the offending agent on re-exposure for accelerated immunoglobulin production.
- ***T-cell independent response*** is usually seen against organisms covered by a polysaccharide capsule, (e.g. *H. influenza* B, pneumococci, meningococci). This capsule resists ingestion of organism by phagocytes, preventing expression of antigen and T-cell activation. In such cases, naïve B cells themselves recognize the pathogen and get activated to produce antibodies. Antibodies produced against T-cell independent responses are largely of IgM class, and no memory cells develop for anamnestic response on re-exposure.

Immunological Disorders

The term immunological disorders includes three distinct abnormalities, discussed elsewhere:

a. Immunodeficiency states, i.e. *inability to recognize or clear foreign antigens* leading to recurrent or opportunistic infections (Ch 8.2).

b. Hypersensitivity reactions, i.e. *inappropriate or disproportionate immune response*, which may be predominantly IGE mediated, IgM/IgG mediated or cell-mediated (Ch 8.4).

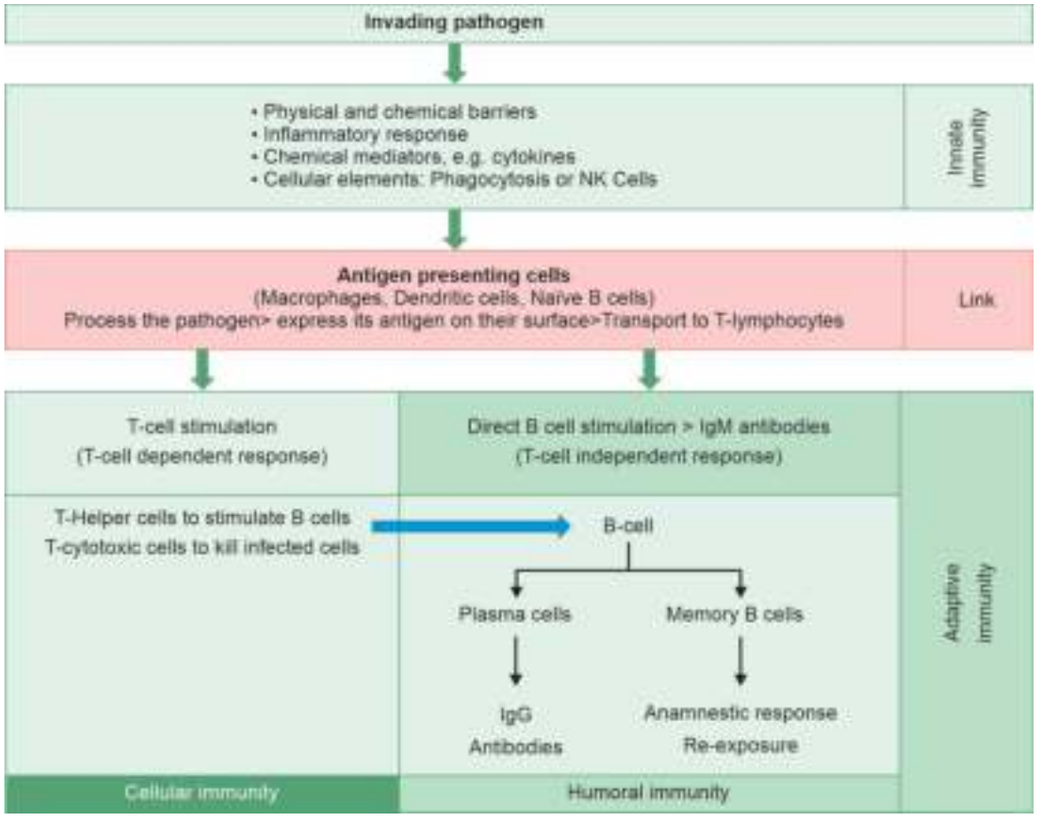

Fig. 8.1: Immunological defense mechanisms.

TABLE 8.1: Common immunodeficiency disorders/states in children

Primary or inherited	*Secondary or acquired*
A. Phagocytic defects	***A. Developmental***
– Cyclic neutropenia	– Prematurity
– Chronic granulomatous disease of childhood	– Newborns (? complement deficiency)
– Chediak-Higashi syndrome	***B. Nutritional***
– Lazy leukocyte syndrome	– Protein-energy malnutrition
– Hyper-IgE syndrome	– Zinc deficiency
– Enzyme defects (G6PD, myeloperoxidase)	***C. Infections***
B. Primary T cell defects	– HIV/AIDS
– DiGeorge syndrome	– *Others:* Measles, pertussis
– Chronic mucocutaneous candidiasis	***D. Impaired splenic function***
– Hyper-IgM syndrome	– Asplenia
C. Primary B cell defects	– Splenectomy
– Transient hypogammaglobulinemia	– *Dysfunction:* Sickle cell disease
– X-linked (Bruton) agammaglobulinemia	***E. Iatrogenic***
– Common variable immunodeficiency	– *Drugs:* Steroids, cytotoxic agents
– Selective IgA/IgG subclass deficiency	– Irradiation
D. Combined B and T cell defects	– Organ transplantation
– Severe combined immunodeficiency (SCID)	***F. Miscellaneous:***
– Wiskott-Aldrich syndrome	– *Protein-loss:* Nephrotic syndrome, burns
E. Complement defects (rarely primary)	– *Metabolic:* Diabetes mellitus, uremia
– Hereditary angioedema	

c. Autoimmune disorders, i.e. *inability to recognize self-antigen* that triggers the immune reactions against own tissues, e.g. rheumatoid disorders (Ch 24).

8.2 IMMUNODEFICIENCY DISORDERS

Increased susceptibility to usual or unusual infections (opportunistic infections) is the clinical hallmark of immunodeficiency disorders. These disorders may involve qualitative *or* quantitative deficiency of any one *or* more component of the immune system **(Table 8.1)**. For the sake of discussion, immunodeficiency disorders may be broadly divided into two categories:

a. Primary immunodeficiency disorders (PID) are rare genetic defects with overall frequency of ~1/10,000 children, including B-cell defects (50%), T-cell defects (30%), phagocytic disorders (18%) and complement disorders (<2%). Family history of similar illness or consanguinity is often present in these cases. Till date over 400 PIDs are known and the list is expanding. **Table 8.2** lists warning signs for suspecting PIDs in children.

b. Secondary immunodeficiency states are relatively more common and usually involve more than one component of immune system. *Viral infections*, e.g. measles, *malnutrition* and *steroid therapy* are three important causes of transient immunodeficiency, while more severe and persistent defects are seen in HIV/AIDS, splenic dysfunction and malignancies.

Common congenital immunodeficiency disorders are discussed here, while acquired defects have been discussed in relevant chapters on primary diseases.

TABLE 8.2: Warning Signs for Primary immunodeficiency disorders (PID) in children

- Four or more new ear infections within one year
- Two or more serious sinus infections within one year
- Two or more months on antibiotics with little effect
- Two or more pneumonias within one year
- Failure of an infant to gain weight or grow normally
- Recurrent, deep skin or organ abscesses
- Persistent thrush in mouth or fungal infection on skin
- Two or more deep-seated infections including septicemia
- Family history of primary immunodeficiency (PID)

I. Phagocytic Disorders

Phagocytic disorders include *quantitative* phagocytic cell deficiency, e.g. neutropenia or *qualitative* functional defects of these cells.

Clinically, these defects usually present with recurrent mucus membrane infections, e.g. gingivitis, *or* superficial/deep abscesses due to pyogenic or gram-ve organisms. *Absence of pus formation despite severe infection is a hallmark of leukocyte migration defect.* Other indicators of phagocytic disorders are *poor wound healing* and *delayed separation of umbilical cord* in newborn.

Diagnosis of phagocytic defects depends on: (a) abnormal neutrophil count and morphology, (b) nitroblue tetrazolium test for intracellular phagocytic capacity, and (c) *in vitro* tests for neutrophil functions, e.g. chemotaxis, phagocytosis and microbiocidal activity.

Persistent neutrophilia or persistent neutropenia are indicative of leukocyte adhesion deficiency-I or severe congenital neutropenia-II important phagocytic defects, respectively.

Management of these disorders include: (a) Long-term antibiotic prophylaxis or recombinant interferon (IFN-γ) therapy, (b) colony stimulating factors (G-CSF, GM-CSF) in leukopenic states, and (c) stem cell transplantation in selected cases.

Some important inherited phagocytic disorders are as follows:

Chronic granulomatous disease of childhood (CGDC) is an X-linked or autosomal recessive disorder, characterized by defective intracellular killing of microbes within phagocytes due to abnormal oxidative metabolic responses. Most cases present in early infancy with: (a) serious, recurrent or persistent infections, (b) perioral/anal eczema, and (c) hepatosplenomegaly.

Chédiak-Higashi syndrome is an autosomal recessive disorder of defective chemotaxis, degranulation and intracellular killing. Apart from recurrent infections in early childhood, these cases are associated with: (a) oculocutaneous albinism, (b) neurological abnormalities, e.g. mental retardation, pyramidal/cerebellar signs, peripheral neuropathy, etc. and (c) neutrophils with *giant cytoplasmic granules.*

Cyclic neutropenia is an autosomal dominant disorder, characterized by *cyclical fluctuations in peripheral neutrophil counts* between normal and neutropenic values (<500/mm^3) with mean oscillatory period of 21 days. During neutropenic phase, child may suffer from mild problems, e.g. oral ulcers, pharyngitis, lymphadenopathy, etc. *or* more serious infections, e.g. pneumonia. Cycles become less noticeable with advancing age, changing into chronic neutropenia.

Hyper IgE syndrome (Job's syndrome) is a rare disorder of chemotaxis and opsonization, characterized by elevated IgE levels (>2000 mg/dl), eosinophilia, recurrent staphylococcal abscesses of skin/deeper tissues and atopic dermatitis.

Lazy leukocyte syndrome is a rare disorder of chemotaxis and neutrophil migration from bone marrow, despite adequate bone marrow reserves.

II. Complement Disorders

Complement disorders are rarely congenital, seen more commonly as acquired defects due to:

- *Deficient production*, e.g. in newborns, PEM and chronic liver diseases,
- *Defective function*, e.g. in sickle cell disease,
- *Increased consumption or loss*, e.g. in septicemia, burns, SLE and nephrotic syndrome.

Clinically, these cases present with recurrent pyogenic or neisserial infections, frequently associated with immune complex disorders (lupus-like illness) and vasculitis syndromes.

Diagnosis is established by assessing CH_{50} activity with control or direct C_3–C_4 immunoassays. Genetic workup is needed to identify inherited complement disorders, most of whom are autosomal recessive except *properdin deficiency* (X-linked).

Management is non-specific, as complement replacement therapy is not available and includes: (a) prolonged antibiotic therapy during infections and (b) immunization against capsular organisms, e.g. pneumococci or meningococci.

Hereditary angioedema is an important autosomal dominant defect of *C_1 inhibitor deficiency* with unrestricted complement activity. Clinically, these cases presents with recurrent self-limiting episodes of non-pitting edema due to vasodilatory effect of kinins released by uncontrolled breakdown of C_4 and C_2. Each attack lasts for 2–3 days and may be fatal. Antihistaminics and steroids are not effective and acute attacks need to be treated with supportive measures, e.g. tracheostomy. Prophylactic oral attenuated androgen (stanozolol) therapy may be useful in frequently recurrent cases.

III. B-Cell Disorders

B-cell disorders, also termed *humoral deficiency states*, may involve all or selective antibody classes, either due to abnormal B-cell differentiation (quantitative) *or* inability to respond against a specific antigen (qualitative). Many cases are secondary to T cell defects.

Clinically, these cases present with variable severity of recurrent sinopulmonary infections or bacteremia, usually due to encapsulated organisms, e.g. *S. pneumoniae, H. influenzae* and *Staph. aureus*. *These disorders do not manifest in first 3 months of life* due to presence of transplacental antibodies from mother.

Diagnosis is usually established by measured nonspecific immunoglobulin levels or specific antibody titers after vaccination, e.g. DPT.

Management of these cases includes: (a) IVIG therapy (400–500 mg/kg/month) and (b) prophylactic antibiotics. Some important and common B-cell disorders are as follows:

Transient hypogammaglobulinemia indicates developmental delay in immunoglobulin production during early infancy, perhaps due to delayed maturation of T helper cells. This leads to accentuated physiological nadir in immunoglobulin levels at 3–5 months (<200 mg/dl), with spontaneous recovery by 18–24 months.

Bruton (X-linked) agammaglobulinemia, seen only in males, is a maturation defect from pre-B-cell stage to mature B-cell stage, characterized by severe hypogammaglobulinemia and absence/hypoplasia of lymphoid tissue, manifesting in late infancy or early childhood.

Common variable immunodeficiency disorder (CVID) is a maturation defect from mature B-cell stage to plasma cell differentiation, characterized by: (a) late onset after the first decade of life, (b) normal or enlarged lymphoid tissue, (c) frequently associated with splenomegaly, autoimmune disorders, e.g. thrombocytopenic purpura or haemolytic anemia, and malignancies.

Selective IgA deficiency is commonest (1:600) but rarely a symptomatic B-cell defect, characterized by low serum IgA levels (<5–10 mg/dl). Symptomatic cases present with recurrent sinopulmonary infections, food allergy and autoimmune/rheumatologic disorders.

Hyper IgM syndrome is characterized by inability to produce antigen-specific antibody response despite elevated IgM and normal IgG/IgA levels, due to a genetic T-cell defect in activating B-cell response. Apart from sinopulmonary infections, hematologic autoimmune disorders or intracellular infections, e.g. tuberculosis are common.

IV. T-cell Disorders

T-cell defects present with widest clinical spectrum, due to their role in activating almost all immunological components.

Clinically, these patients usually present with: (a) fungal or intracellular infections, e.g. mycobacteria, due to defective phagocytic activation, (b) viral infections due to decreased NK-cell activity, and (c) opportunistic infections due to impaired B cell activation and immunoglobulin production.

Diagnosis of T cell defects depend on quantitative T cell and sub-cell counts, *in vivo* T-cell function tests, e.g. tuberculin test, candida skin test, phytohemagglutination assay (PHA), and *in vitro* tests, e.g. lymphokines assay, etc. Many of these defects may be diagnosed prenatally, e.g. Severe combined immunodeficiency disorders or Wiskott-Aldrich syndrome.

Treatment of choice for severe T-cell defects is bone marrow transplant, though gene therapy has been successful in some cases. IVIG therapy is indicated in cases with co-existing humoral immunodeficiency. Common T-cell defects are rarely isolated, usually associated with other immune disturbances and include:

DiGeorge syndrome is characterized by: (a) thymic aplasia due to 3rd/4th pharyngeal arch dysgenesis, (b) hypocalcemic tetany due to parathyroid dysgenesis, (c) cardiac cono-truncal *or* aortic arch abnormalities, e.g. Fallot's tetralogy or truncus arteriosus, *and* (d) typical facial features with micrognathia, hypertelorism, notched pinna, lowest ears, etc., apart from T cell defects of variable severity.

Severe combined immunodeficiency disorders (SCID) is a heterogeneous group of genetic disorders, characterized by: (a) absent T-and NK-cells in peripheral blood, (b) severe hypogammaglobulinemia despite normal B cell count, and (c) severe lymphoid hypoplasia. Most cases present since neonatal period with failure to thrive, severe bacterial infections, chronic mucocutaneous candidiasis, intractable diarrhea, opportunistic infections, e.g. *Pneumocystis jiroveci* pneumonia and eczematous skin disorders.

Wiskott-Aldrich syndrome is an X-linked defect of T-and B-cell dysfunction, associated with thrombocytopenia and eczema. IgE and IgA levels are raised, with low IgM levels. Most patients manifest in early infancy with severe bleeding *or* opportunistic/recurrent infections.

Chronic mucocutaneous candidiasis is an autosomal recessive defect of T-cell proliferation and function with normal B-cell count, presenting as chronic/recurrent mucocutaneous candidiasis in early childhood, with autoimmune endocrinopathies, e.g. Addison's disease or hypoparathyroidism.

8.3 OPPORTUNISTIC INFECTIONS

Opportunistic infections (OIs) are defined as *"infections with unusual frequency, microbial etiology or natural course, in a host with impaired normal defence mechanisms".*

Incidence of these infections has substantially increased in recent years due to better survival of immunocompromizsed patients, increasing use of invasive devices, implants, transplants and use of immunosuppressive therapy, etc., along with better diagnostic facilities.

OIs may manifest as: (a) recurrent infections by common organisms, or (b) single or recurrent infections by pathogens, normally considered as non-pathogenic, *or* (c) unusual course or treatment resistance of a common infection.

Recurrent infections are otherwise also common in early childhood due to environmental factors, and *all cases of recurrent infections do not indicate impaired host-defence*.

Predisposing factors: Normal host-defence mechanisms include many physical *or* immunological barriers against infections. Any congenital or acquired disease *or* environmental factor that impairs one or more of these barriers may cause OIs **(Table 8.3)**. Thus, all OIs do not necessarily mean immunosuppressive state and many of them are due to impaired anatomical or physiological barriers.

Microbial etiology: Any organism is a potential pathogen in immunocompromised host. Common microbial profile of OIs includes infections due to:

- Low virulence organisms from normal human flora, e.g. coagulase negative staphylococci, enterococci, etc.
- Organisms generally considered as non-pathogenic in normal settings, e.g. *Pneumocystis jiroveci, Candida*, etc.

TABLE 8.3: Predisposing factors for opportunistic/recurrent infections

a. Impaired skin/mucosal barriers
- Congenital dermal sinuses and tracts
- *Acquired:* Burns, trauma and surgery
- *Foreign body:*
  - *Catheters:* Vascular, urinary, dialysis catheter
  - *Implants:* VP shunts, cardiac/orthopedic devices
- ? Vitamin A deficiency

b. Impaired mechanical clearance
- *Mucus drainage:* Cystic fibrosis, undrained cavity
- *Ciliary function:* Post-viral, Immotile cilia syndrome

c. Altered normal flora
- Prolonged/partial antibiotic therapy

d. Congenital immunodeficiency states
- Phagocytic disorders
- B- or T-cell defects
- Complement deficiency
- *Impaired local immunity:* IgA deficiency

e. Acquired immunodeficiency states
- Severe malnutrition
- *Post-infective:* Measles, pertussis
- HIV/AIDS
- *Disease:* Malignancy, sickle cell disease
- *Iatrogenic:* Transplants, drugs*, splenectomy

*For example, anti-malignancy drugs, antibiotics, steroids.

- Organisms prevalent in local hospital setting, e.g. *Pseudomonas*, *Klebsiella*, etc.
- Polymicrobial infections, and
- Multi-drug resistant infections.

Clinical spectrum of OIs depends on the primary etiology, site of infection, causative pathogen and extent of immunosuppression. However, some general characteristics are as follows:

- Fever is a sensitive, specific and often the only sign of OIs. Contrary to general view, febrile response is rarely masked, even in severe immunocompromised states.
- Other signs of infection or inflammation, e.g. erythema, exudation, etc. may be minimum or absent in immunocompromised host. These cases may have severe pneumonia with normal X-ray, meningitis with normal CSF and cellulitis without swelling.
- Frequency and severity of OIs directly correlates with severity indicators of immunosuppression, e.g. neutrophil counts (<500 mm^3) or CD_4 counts.
- OIs are usually generalized or multi-systemic, except tissue-tropic infections, e.g. *P. jiroveci* pneumonia or Cryptosporidium diarrhea.
- Serological tests, e.g. antibody titers or skin tests, e.g. tuberculin test, are unreliable in these cases and negative tests do not exclude corresponding infection.

Some important OIs are as follows:

A. OIs due to impaired physical barriers: Skin and mucus membranes are not only the physical barriers but also offer mechanical (mucociliary clearance), chemical (bacteriostatic fatty acids in skin), enzymatic (lactoferrin, lysozyme secreted by mucus membranes), immunological (secretory IgA in mucus membranes) and microbial (normal colonizing flora) protection against infections. These barriers may be impaired in congenital anomalies, e.g. dermal sinuses/tracts or acquired lesions, e.g. trauma, surgery, burns, etc.

- *Burns* patients are susceptible for OIs due to broken skin/mucosal barriers, presence of necrotic tissue and altered normal flora following antimicrobial therapy or vascular catheterizations. Most of these infections are caused by nosocomial or human flora pathogens, e.g. *Pseudomonas*, *Staph. aureus* or CONS and present with severe septicemia or pneumonia.
- *Surgical infections* are at specific risk for anaerobic infections, due to migration of normal colonizing flora at wound-sites.
- *Dermal sinus tracts* are usually colonized or infected by *Staph. epidermidis* or *diphtheroids*.

B. Device-related infections: Indwelling vascular/other catheters, shunts and implants act as nidus for localization of infection or the infection may be introduced at the time of insertion.

- *Vascular catheter-related infections* are more common with central than peripheral lines, risk being directly proportional to the duration of cannulation. Over half of them are caused by *Staph. epidermidis*, followed by gram-negative bacilli and Candida. Frequent change of catheters and catheter site is essential to prevent these infections. Diagnosis is based on identical growth on blood and catheter-tip culture.
- *CSF shunt infections* are predominantly caused by *Staph. epidermidis* (>70%) and present with: (a) shunt colonization, (b) shunt infection with wound infection/dehiscence, (c) shunt infection with ventriculitis, and (d) shunt infection with peritonitis. Shunt removal is often necessary, followed by antibiotics. *Vancomycin* is the drug of choice for shunt infections.
- *Urinary catheter-related infections* are common with indwelling catheters, usually caused by gram –ve bacilli or enterococci. These cases present with persistent bacteriuria or symptomatic urinary tract infections. Catheter removal alone is sufficient for asymptomatic bacteriuria, while antibiotics are necessary in symptomatic cases. Prophylactic antibiotics do not reduce the risk of catheter-related urinary tract infection.
- *Peritoneal dialysis catheter-related infections* are usually due to *Staph. epidermidis or aureus* and present with local *exit-tunnel infection* or peritonitis. Vancomycin *with* a third generation cephalosporin or aminoglycoside is the drug of choice in these cases.
- *Orthopedic or cardiac valvular implants* are usually infected by CONS or *Staph. aureus*, presenting as wound infection or endocarditis, respectively.

- *OIs due to nebulization/ventilator therapy* usually present with pneumonia due to *Pseudomonas, Serratia* or legionella.

C. Acquired immunodeficiency states may be due to the disease, (e.g. PEM, HIV, malignancy) or iatrogenic (steroid/cytotoxic therapy, splenectomy, bone marrow transplants).

- *Severely malnourished children* are prone for gram-negative septicemia as well as severe disease with common infections, e.g. measles, varicella and tuberculosis, due to impaired T cell function, phagocytic activity and complement activity.
- *Post-infective transient immunosuppression* for 2–3 months is common after measles and pertussis infection, which may lead to reactivation of underlying tuberculosis.
- *Transplanted individuals* are highly susceptible for OIs due to immunosuppressive drug/radiation therapy, prolonged invasive devices, surgical injury, and graft versus host disease (GVHD). The type of OIs in these cases depends on time-course of transplant—bacterial infections in pre-operative preparatory phase, anaerobic infections in peri-operative period, *and* viral (CMV, RSV) or PCP infections in post-operative period. While septicemia and pneumonia is common in marrow transplants, children with renal/liver transplant are additionally susceptible for urinary tract infections and cholangitis, respectively.
- *Malignancy* is a common cause of OIs due to primary *or* iatrogenic immunosuppression as well as nosocomial infections. Microbial profile in these cases varies according to absolute neutrophil counts, as follows:
  - *Non-neutropenic cases:* Viral and fungal infections, PCP and toxoplasmosis.
  - *Neutropenic cases:* Serious bacterial infections due to gram +ve cocci, e.g. *Staph. aureus,* CONS, enterococci, etc. *or* gram-negative bacilli, e.g. Pseudomonas, Klebsiella, etc.
    Note that meningitis is unusual in granulocytopenic patients.

D. Inherited immunodeficiency disorders are rare (Ch 8.2), but should be suspected in cases with warning signals **(Table 8.2)**, *without an acquired cause* for impaired host-defence.

Diagnostic evaluation of suspected OI aims to confirm the microbial etiology as well as to identify the predisposing factors and includes:

- ***History,*** including: (a) review of medical records to confirm the frequency and nature of recurrent infections, (b) family history of similar illnesses, TB/HIV or consanguinity (for inherited defects), (c) past history of immunosuppressive infections, e.g. measles, pertussis, etc. (d) treatment history of prolonged steroid/cytotoxic therapy or splenectomy, and (e) epidemiological history for environmental causes for recurrent infections.
- ***Pattern of infections*** may provide important clues to the nature of immunodeficiency, as follows:
  - Recurrent bacterial infections indicate probable B-cell defects.
  - Atypical course of mycobacterial, viral, fungal or intracellular infections, e.g. toxoplasmosis indicate probable T-cell defects.
  - Recurrent staphylococcal or gram-ve infections, as well as mucocutaneous infections indicate probable defects in phagocytosis, which are also characterized by *inadequate pus production*.
  - Recurrent infections due to capsular organisms, e.g. Pneumococci, *H. influenzae* or Salmonella indicate splenic dysfunction or complement deficiency.
- ***Co-existing illnesses*** are important diagnostic clues for secondary immunodeficiency disorders (malignancies, malnutrition, sickle cell disease, nephritic syndrome) as well as inherited immunodeficiency disorders **(Table 8.4)**.
- ***Laboratory evaluation*** in these cases includes baseline screening tests for common defects and search for microbial etiology, followed by more selective investigations, guided by clinical suspicion **(Table 8.5)**.

Management depends on the identified cause, though some broad principles in management of immunocompromised children include:

- Avoidance of unnecessary microbial exposure, e.g. overcrowding.
- Avoidance of live vaccines in severe cases.

TABLE 8.4: Physical indicators of inherited immunodeficiency disorders

Typical facies	*DiGeorge syndrome*
Albinism	*Chédiak-Higashi syndrome*
Atopic dermatitis	*T-cell or phagocytic defects*
Alopecia	*SCID*
Red hair	*Job's syndrome*
Persistent thrush	CMC
Absent tonsils	*SCID, XL agammaglobulinemia*
Large tonsils/LNs	*CVID*
Telangiectasia	*Ataxia telangiectasia*
Weeping ears	*CGD, Wiskott-Aldrich syndrome*
Hepatosplenomegaly	*CGD*
Recurrent respiratory infections	*Hypogammaglobulinemia*
Thrombocytopenia	Wiskott-Aldrich syndrome

SCID: Severe combined immunodeficiency disorders; **CMC:** Chronic mucocutaneous candidiasis; **CGD:** Chronic granulomatous disease; **CVID:** Common variable immunodeficiency

TABLE 8.5: Laboratory investigations in OIs

Step I: Base line screening tests:
- *Hematological:*
  - Leukocyte count[1]
  - Leukocyte morphology[2]
  - Platelet count[3]
  - Howell-Jolly bodies[4]
  - ESR for chronic infection, TB
- *Radiological:* Chest, sinuses, mastoid, etc.
- Microbiological cultures from suspected sites
- *Immunological tests:* Serology, TT (unreliable)
- Relevant tests for predisposing illness

Step II: Specific immunological screening tests:
- *Suspected B-cell defects*
  - S. IgA, IgG and IgM levels[5]
  - S. IgG subclass measurements
  - Isohemagglutinin (anti-A and B) titers[6]
  - Vaccine-antibody titers (tetanus, diphtheria)[7]
  - B-cell count
- *Suspected T-cell defects (Only if ALC is low)*
  - T-subpopulation count (by flow cytometry)
    Absolute CD4 count
    CD4/CD8 ratio (N: >4:1)
    NK cell counts
  - T-cell function tests
    In vivo: Tuberculin, candida skin tests
    In vitro: Lymphokines assay
- *Suspected phagocytic defect*
  - Nitroblue tetrazolium dye test (NBT)
  - Leukocyte function tests
- *Suspected complement deficiency*
  - CH_{50} activity with control
  - Direct C_3–C_4 immunoassays

Step III: Molecular tests (inherited defect)
  - Index case
  - Prenatal diagnosis

[1]Neutropenia, T-cell defects, eosinophilia in hyper IgE syndrome
[2]Abnormal in Chédiak-Higashi syndrome
[3]Thrombocytopenia in Wiskott-Aldrich syndrome
[4]In splenic dysfunction or asplenia
[5]Hypergamaglobulinemia indicates HIV or CGDC;
[6]Indicative of IgM function
[7]Indicative of IgG function

- Prophylactic vaccinations for capsular organisms, e.g. pneumococci, meningococci, *H. influenzae*, etc.
- Prophylactic *or* early antimicrobial therapy.
- Adequate drainage of infection site, e.g. abscess, empyema, etc.
- Replacement therapy with plasma (complement deficiency) or IV immunoglobulins in select cases.
- Specific therapy *or* bone marrow transplantation (T-cell defects), interferon, etc.

8.4 HYPERSENSITIVITY DISORDERS

8

Hypersensitivity, in context of immunology, denotes *untoward and inappropriate immunological response* to a foreign antigen involving antigen-specific antibodies and memory cells. According to immunopathogenesis, hypersensitivity reactions may be divided into four types:

1. Type I (IgE mediated) reactions, also termed allergy, are triggered by the binding of an allergen to *specific or reaginic IgE antibodies* attached on the surface receptors of circulatory basophils and tissue mast cells. (Ch 8.4.1)

2. Type II (cytotoxic) reactions are characterized by abnormal binding of IgM or IgG antibodies to *self-antigens*, modified by external insult, (e.g. drugs or infections), with complement activation and consequent target tissue injury. Discussed in relevant chapters, these reactions are usually *tissue-specific*, e.g. autoimmune hemolytic anemia or thrombocytopenia (target antigen-cell membrane), myasthenia gravis (target antigen-acetylcholine receptor) or Graves' disease (target antigen-TSH receptors).

3. Type III (immune-complex) reactions involve formation of soluble antigen-antibody complexes, which are either removed to reticuloendothelial organs or deposited at target tissues, e.g. glomerular basement membrane, skin and synovium. Immune-complex mediated complement activation leads to attraction of polymorphs at these sites with local inflammatory reactions and tissue damage, i.e. *Arthus reaction;* or more systemic and widespread reactions, i.e. **serum sickness.** Other common examples of these reactions are proteinuria in nephrotic syndrome and vasculitis syndromes, e.g. Henoch-Schönlein purpura.

Serum sickness presents as fever, arthralgia, urticaria, lymphadenopathy and proteinuria, usually after 7–14 days of the administration of animal-derived antisera, e.g. equine anti-snake venom, anti-tetanus serum, etc. or drugs, e.g. penicillin, cephalosporins, etc.

4. Type IV (delayed hypersensitivity) reactions are mediated by antigen-specific T cells and macrophages, due to recognition of antigen-peptide on antigen processing cells by T memory cells and release of inflammatory cytokines. These reactions peak after 24–48 hours of antigen exposure and include tuberculin reactions, contact dermatitis, transplant rejection and graft *versus* host disease, etc.

8.4.1 GENERAL CONCEPTS IN ALLERGY

Allergy denotes a specific type of hypersensitivity reactions mediated by IgE antibodies and provoked by specific antigens, i.e. allergens.

Allergen denote a substance capable of inducing IgE mediated reactions on exposure. The term allergen and antigen are not synonymous, as all allergens are not good antigens, (e.g. rag-weed pollens) and conversely all antigens are not necessarily allergens, (e.g. vaccines).

Atopy denotes an *inherited or familial predisposition* for allergic disorders.

General pathophysiology: Allergic reactions are triggered by the binding of an allergen to specific or

reaginic IgE antibodies, attached on the surface receptors of circulatory basophils and tissue mast cells.

These reaginic antibodies are formed after an earlier exposure to same allergen, i.e. *sensitization*. On subsequent exposure, antigen-IgE binding on the surface of basophils/mast cells provokes two different types of reactions:

a. ***Early-phase reactions*** within 20 minutes, due to degranulation of mast cells and release of pre-formed chemical mediators, e.g. histamine and eosinophil chemotactic factors, presenting as urticaria, pruritis, sneezing, wheezing and hypotension, e.g. anaphylaxis, asthma, allergic rhinitis or insect allergy.
b. ***Late-phase reactions*** after 4–12 hours, due to influx of other allergic (basophils, eosinophils, mast cells) and inflammatory cells (polymorphs, lymphocytes) at the site of allergen exposure and consequent release of other chemical mediators, e.g. leukotrienes and prostaglandins. These mediators amplify allergic inflammation and facilitate further differentiation of allergic cells and IgE-producing B cells. Late-reactions have been implicated in development of long-term nasobronchial hyperreactivity in allergic individuals.

General principles in diagnosis: Clinical spectrum of allergic disorders is extremely wide, ranging from life-threatening *anaphylaxis* to system-specific disorders, e.g. *asthma, allergic rhinitis, atopic dermatitis or urticaria*. Allergic disorders are usually characterized by following common features:

- Chronic course with intermittent exacerbations.
- Cause-effect relationship with allergen.
- Family history of atopic disorders.
- *In vitro* laboratory abnormalities, e.g.
  - Peripheral eosinophilia (AEC >600 cell/mm^3)
  - Presence of eosinophils in body secretions
  - Elevated IgE levels (N: 10–20 IU/ml)
  - Presence of allergen-specific IgE antibodies
- *In vivo* positive challenge tests, e.g.
  - Allergen skin testing
  - Provocation tests.

Allergen skin test is an important diagnostic tool to identify causative allergen in many allergic disorders, e.g. asthma or allergic rhinitis. These tests involve intradermal injections of miniscule quantities of a battery of commercial available allergens, (e.g. mites, dusts, pollens, danders and fungi), along with a negative (saline) and a positive (histamine) control, over forearm or back. Local response to each allergen injection, i.e. erythema and wheel size is noted and compared with controls, after 10 minutes (*early response*) and 2–3 hours (*late response*). Severity of response indicates strength of cause-effect relationship, though false-positive and false-negative results are common and results must be correlated with clinical observations.

Provocation or challenge tests involve deliberate exposure of the affected mucus membrane to suspected allergen, which may induce the allergen-specific clinical reaction. Commonly used provocation tests include *bronchial provocation test* in asthma (nebulization of suspected allergen to see spirometric changes) and oral provocation tests in food allergy or atopic dermatitis (ingestion of suspected food item to see reappearance of diarrhea or skin lesions). Although useful in cases with equivocal *in vitro* laboratory results or skin testing, these tests are rarely used due to the risk of life-threatening reactions.

General principles of management in allergic disorders include: (a) avoidance of suspected allergens if possible; (b) immunotherapy (desensitization) against unavoidable allergens; (c) specific pharmacotherapy to block the release or action of chemical mediators.

While specific therapeutic measures in management of individual allergic disorders have been discussed in respective chapters, some general principles are as follows:

a. Avoidance of allergens: Common allergens may be divided into 3 categories:

1. Inhalant allergens, e.g. pollens, dust, dust-mite, danders and fungi,
2. Ingestant allergens, e.g. food, and
3. Contactant allergens, e.g. synthetic fabrics or elastics.

In addition, viral infections and smoke exposure, though not allergenic by themselves, are common triggering events for precipitation of acute attacks in children.

As the dictum goes, *anything above the earth and below the sky may be allergenic*. Further, atopic children are often allergic to many allergens at the same time. Considering this biological diversity, it is often difficult to identify and avoid specific allergens, though following precautions may be helpful:

- *Avoidance of outdoor allergens*, e.g. dust exposure, visit to flowery gardens, etc.
- *Avoidance of indoor allergens* with wet mopping of floor (dust); removal of indoor plants, soft toys and carpets (mites), avoidance of pets (danders), regular cleaning of AC filters (fungi), pest control (cockroaches), etc.
- *Avoidance of suspected dietary substance*s is often overemphasized, without much scientific basis. However, a proven cause-effect observation with particular food stuff may be indication to avoid canned foods with preservatives, coloring agents, etc.
- *Avoidance of other triggering factors*, e.g. smoke exposure, viral infections, etc.

b. Immunotherapy: Some allergens are unavoidable, e.g. pollens, dust mites, etc. Immunotherapy is an option to desensitize the child against these identified but unavoidable allergen/s, by repeated intradermal

injections of the increasing dose of allergen/s as an aqueous extract (up to 10 allergens may be combined in same solution), once/twice a week (interval is increased gradually), till the optimal maintenance dose is reached and continued for another 3–6 months.

Although with a sound physiological basis, immunotherapy is often ineffective due to: (a) inadequate quality and unknown doses of currently available commercial allergen extracts, (b) frequent reappearance of hypersensitivity after discontinuation of maintenance doses, (c) change-over hypersensitivity from one to another allergen in inherently atopic child, and (d) poor compliance to multiple injections. However, it may be tried in selected cases of asthma or allergic rhinitis, where avoidance of suspected allergen is not possible.

c. Pharmacotherapy of allergic disorders may be broadly divided into *preventors*, i.e. drugs to prevent the attacks and *rescuers*—drugs to combat acute response. These drugs aim to:

- *Block the release of chemical mediators*, e.g. mast cell stabilizers, e.g. cromolyn sodium, nedocromil sodium, lodoxamide, olopatadine (last two for topical use only in allergic conjunctivitis),
- *Block the action of these mediators*, e.g. antihistaminics, steroids, leukotriene inhibitors, (montelukast, etc.)
- A*ntagonise the physiological response of mediators*, e.g. β-agonists, acetylcholine inhibitors, etc.

While first two groups of drugs prevent the allergic attack and are used on long-term basis, the last group is useful only to control acute clinical manifestations. Important pharmacological agents in various atopic disorders have been discussed in respective chapters.

Antihistamines are competitive antagonists for H_1 histamine receptors, more effective in preventing than reversing the action of histamine. Consequently, these drugs are more effective in preventing, rather than treating, an established attack. As histamine is not the only chemical mediator of allergic response, these drugs are poorly effective in asthma or atopic dermatitis.

However, antihistamines are extremely valuable in the management of acute allergic rhinitis or anaphylaxis which are predominantly histamine-mediated. While large number of antihistamines are available with near-comparable efficacy, second generation histamines, e.g. cetirizine, loratidine, terfenadine are preferable due to less side-effects, e.g. drowsiness.

8.4.2 ANAPHYLAXIS

Anaphylactic reactions are acute, life-threatening hypersensitivity reactions, provoked by variety of injected, inhaled or ingested foreign substances. Note that the term *anaphylactoid reaction* denotes clinically similar reactions to certain agents, e.g. radio-contrast dyes, which are *not* immunologically mediated.

TABLE 8.6: Precipitating agents for anaphylaxis

- Drugs, e.g. *penicillins, blood, equine sera, etc.*
- Foods, e.g. *sea-food, egg, nuts, additives, etc.*
- Insect stings and venoms
- Biological contact agents, e.g. *latex, wool, etc.*
- Exercise-induced
- Idiopathic

Causes: Common precipitating agents for anaphylaxis are enumerated in **Table 8.6**, though the cause remains unidentified in many cases.

Pathogenesis: Anaphylactic reactions are type I hypersensitivity reactions, mediated by specific IgE antibodies, formed in response to previous sensitization. These antibodies are present on surface of basophils and mast cells and subsequent exposure to the same allergen leads to degranulation of mast cells and release of numerous chemical mediators.

Final effect of these mediators may manifest immediately with a few minutes (*acute phase reaction*) or after many hours (*late phase reaction*), with *three main clinical components* of anaphylaxis—acute bronchospasm, increased vascular permeability and increased secretory activity of mucous glands.

Clinically, these reactions usually begin within few minutes of exposure to offending allergen, presenting with sudden onset of:

- *Dermatologic manifestations* involving skin and mucus membranes, e.g. urticaria, pruritus, flushing, perioral tingling, red/itchy eyes, sneezing/rhinorrhea and extreme diaphoresis;
- *Respiratory manifestations,* e.g. wheezing, stridor and/or respiratory distress;
- *Cardiovascular manifestations,* e.g. hypotension, bradycardia or shock and a general feeling of sinking or impending doom, with rapidly developing unconsciousness.
- *Gastrointestinal manifestations* in some cases with abdominal cramps, diarrhea and vomiting.

Many cases die rapidly due to airway obstruction or cardio-respiratory arrest, unless treated immediately.

Some patients after initial recovery develop recurrence (*biphasic reaction*) after 6–8 hours due to late-phase reactions.

D/D: While history of exposure to an offending agent and catastrophic clinical picture is characteristic, anaphylaxis needs to be differentiated from: (a) vasovagal attacks, (b) cardiac arrhythmia, (c) foreign body aspiration, (d) hypoglycemia, and (e) acute poisoning. Elevated IgE levels and eosinophilia differentiates anaphylaxis from *anaphylactoid* reactions.

Sudden development of clinical manifestations involving at least two of the three different systems-dermatological,

respiratory and cardiovascular system, is considered as strongly indicative of anaphylaxis.

Management: Anaphylaxis is a life-threatening emergency, which needs immediate resuscitative measures and subsequent hospitalization for at least 24 hours to watch for late-phase reactions. Immediate resuscitative measures include:

- *Subcutaneous adrenaline is the cornerstone of management of anaphylaxis, given as* 1:1000 aqueous preparation (0.1 ml/kg; max 0.5 ml) and repeated every 15–20 minutes till response. In superficial venom injections, e.g. insect stings, half of the SC dose (diluted in 2 ml saline) may be given locally at the site of injection.

  All public vaccination sites are provided with *anaphylaxis kit* containing adrenaline, insulin/tuberculin syringe, 24–25 G needle and instructions about age-wise doses of adrenaline – *0.05 ml < 1 year, 0.1 ml from 1–6 years and 0.2 ml from 6–12 years, 0.3 ml from 12–18 years and 0.5 ml in adults.*
- *Place the child in supine position* and assess the airway, breathing, circulation.
- *Respiratory support* with airway/oxygen/ventilatory support and tracheostomy, if needed.
- *Cardiovascular support* with IV fluids (normal saline 20 ml/kg bolus) and inotropes, e.g. dopamine, if required.
- *Nebulized epinephrine (0.5 ml/kg) or nebulized salbutamol (0.15 ml/kg)* in cases with stridor or wheeze respectively, which may be repeated after 10–15 minutes,
- *Antihistaminics*, e.g. diphenhydramine or chlorpheniramine for next 24–48 hours, have no role in the management of acute attack but may prevent late reactions.
- *Systemic steroids*, e.g. IV hydrocortisone (5 mg/kg 6-hourly), although controversial in acute management, may help to decrease the duration and severity of manifestations.
- If a *precipitating agent*, e.g. drug is identified, a clear warning should be noted on medical records to prevent further episodes.

System-specific allergic disorders, e.g. asthma, allergic rhinitis and atopic dermatitis, etc. have been discussed in respective chapters.

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CHAPTER

9

Immunization

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Since the global eradication of smallpox from May 8th, 1980, immunization has been established as the most cost-effective preventive measure against infectious diseases.

Immunization may be defined as *induction of specific immune response* by either: (a) deliberate inoculation of immunogens to stimulate *in vivo* antibody production ***(active immunization)***, or (b) administration of pre-formed antibodies, i.e. immunoglobulins ***(passive immunization).***

Although frequently used interchangeably, the terms *immunization* and *vaccination* have different connotations. Vaccination denotes a *process* to administer immunogenic agents for active immunization. A vaccinated child may not be considered as immunized, if the desired immune response is not induced due to faulty vaccine or technique.

9.1 BASIC CONSIDERATIONS

The term *immunity* in preventive pediatrics refers to *complete protection or at least partial resistance against an infection*, and may be classified as:

- ***Natural immunity,*** acquired by:
  - Transplacental transfer of maternal antibodies in fetal life, i.e. *natural passive immunity*, or
  - Clinical or sub-clinical infections in postnatal life, i.e. *natural active immunity.*
- ***Artificial immunity,*** acquired by:
  - Disease-specific vaccinations, i.e. *artificial active immunity,* or
  - Administration of specific or non-specific immunoglobulins, i.e. *artificial passive immunity.*

While active immunity persists for many years or even throughout the life, passive immunity does not last for more than few weeks. This chapter concentrates on artificial immunity, specially active immunization via vaccines, followed by some relevant aspects of passive immunization.

9.1.1 PHYSIOLOGY OF IMMUNIZATION

Primary objective of immunization is *to develop and sustain a disease-specific antibody titers above the protective threshold*, by exposing the host-immune system to *a deliberately introduced antigen, devoid of its pathogenic properties,* i.e. *vaccine*. Vaccine-induced antigenic exposure, like natural infection, initiates various host-immune responses, e.g. specific immunoglobulin production (*humoral response*) or T-cell activation (*cellular response*). Complex interaction of these responses has been discussed in Ch 8.1.

Development of protective immunity after vaccination may be considered as a two-step process—primary response and secondary response **(Fig. 9.1)**.

Primary response: After the first dose of vaccine, there is a lag period of several days before antigen-specific antibodies appear in the serum. However, these antibodies are mainly of IgM class with short life-span (21–28 days) and have no long-term protective value. On the other hand, IgG titers start rise after 2–3 weeks and remain high for many months before gradual decline. The most important event during primary challenge is the sensitization of B-cells, some of whom develop as antigen-specific *memory cells* and persist throughout the life.

Secondary response: When a sensitized host is re-exposed to the same antigen by subsequent vaccine-dose or natural infection, pre-existing *memory cells* activate a more rapid and pronounced IgG response, along with the short-lived IgM response. Antibodies titers, achieved during this phase, are much higher than that during the primary response (*anamnestic or booster response*) and remain protective for many years or throughout life.

Thus, the development of adequately protective antibody levels after vaccination requires at least two exposures at different time intervals, necessitating multiple doses, specially for inactivated vaccines. However in case of live vaccines, *in vivo* replication of organisms provides a sustained source of antigen, leading to merger of primary and secondary responses. Hence, usually single dose is enough for live vaccines.

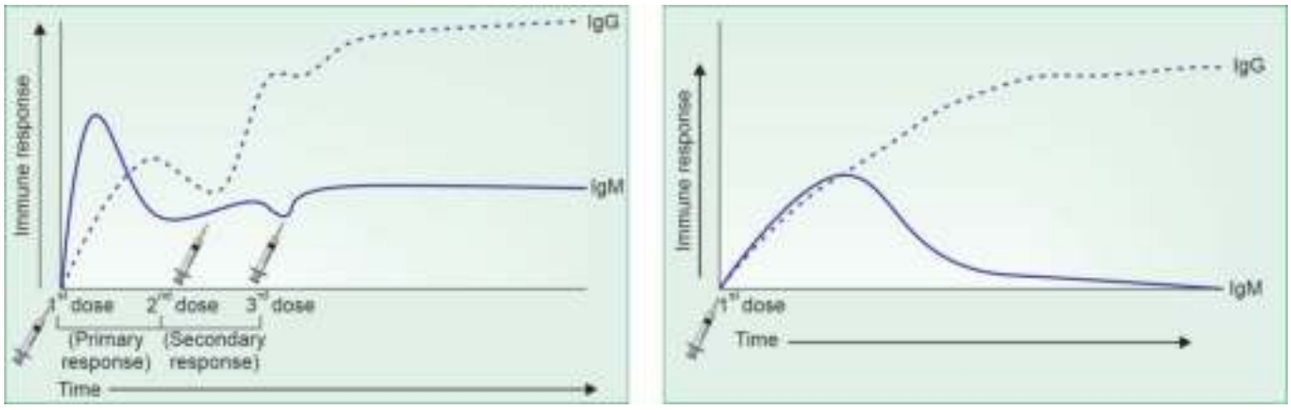

Fig. 9.1: Immune response following immunization with (A) Inactivated vaccines; (B) Live vaccines.

9.1.2 DETERMINANTS OF IMMUNE RESPONSE

Success of vaccination in an individual child is assessed by:

- ***Seroconversion,*** i.e. development of antibodies after administration of a vaccine or more than four-fold rise in pre-vaccination titers, if already present due to previous exposure.
- ***Seroprotection,*** i.e. development of antibodies in the pre-defined titers required for protection from the disease.
- ***Immunogenicity,*** i.e. ability of the vaccine to induce seroprotective titers or desired cell mediated response.
- ***Protective efficacy,*** i.e. ability of the vaccine to actually reduce the risk of disease in vaccinated population as compared to unvaccinated population, denoted in terms of percentage.

In brief, immunogenicity is a laboratory criteria to assess the effect of a vaccine, while protective efficacy is a real-life field result.

Important determinants of success after individual vaccination include:

- ***Type of the antigen:*** Live vaccines are highly immunogenic due to endogenous production of antigen due to *in vitro* multiplication of organisms, as compared to killed, subunit or toxoid vaccines that carry limited antigenic load per dose. Polysaccharide vaccines are poorly immunogenic as they produce only T-cell independent response of mainly IgM class with no development of memory cells, being gradually replaced by conjugated vaccines. Hence, while live vaccines are usually given as a single dose, inactivated vaccines, need multiple primary doses and boosters for adequate and sustained immune response.
- ***Number of doses:*** Increasing the number of doses increases immunogenicity and efficacy of a vaccine, specially in cases of inactivated vaccines. Immunocompromised child are often advised to take additional dose/s of these vaccines. While one dose is generally enough for most of live vaccines, additional dose are frequently advised to ensure better seroprotection, e.g. seroprotection rate after first dose on measles is 95–98% and nearly 100% after two doses.
- ***Dose of the antigen:*** Higher doses of antigen induce better immunity but with higher risk of side effects and hence, increasing the antigen content beyond a limit is not recommended. Still, higher (double dose) vaccinations are sometimes recommended in immunocompromised populations, e.g. for HBV vaccine.
- ***Immune status of host:*** Vaccination in preterms, malnourished and immunocompromised children may not produce adequate immune response due to relative immune incompetence. Although live vaccines may theoretically produce the disease in these cases, such complications are extremely rare and should not preclude the use of live vaccines except in severe immunodeficiency states.
- ***Time-interval between doses:*** A gap of less than one month between two doses of non-live vaccines may not produce adequate secondary response. Although an interval of two months produces best secondary response, need to complete the immunization as early as possible in the baby has necessitated use of one-month interval between two doses of DPT, etc.
- ***Time interval between different vaccines:*** When two live vaccines for different diseases are given at short interval (<1 months), early non-specific immune response to the previous vaccine may interfere with uptake of the subsequent vaccine. Hence, a minimum interval of one month is essential for adequate response to each live vaccine. However, multiple live vaccines, given on the same day produce parallel and adequate immune response for each of them and hence, use of combination vaccines is as effective as separate vaccinations.

No specific time-interval is needed between two inactivated vaccines or one-live and one inactivated vaccine,

barring few exceptions: (a) PCV should always precede PPSV by 8 weeks, when used together, and (b) PCV should precede meningococcal vaccine by 4 weeks, when used together.

- **Presence of maternal antibodies** during first 3–6 months of life interferes with successful active immunization by rapid elimination of the vaccine-antigen. Hence, most childhood immunizations are given after neonatal period. However, BCG (that produces cell mediated immunity), OPV (that produces local immunity) and HBV (maternal antibodies are absent or non-interfering) may be given at birth.

  Maternal antibodies interfere more with response to live vaccines than to inactivated vaccines. Hence, while inactivated vaccines, e.g. DPT, PCV can be given earlier at 6 weeks, live vaccines are usually not given before 9 months of age, e.g. MR or varicella.
- ***Route of administration:*** Parenteral vaccines mainly induce systemic immunity, while oral vaccines, e.g. OPV and Rotavirus vaccines mainly induce local immunity (secretory IgA-mediated). Local immunity prevents the invasion of pathogen itself, while systemic or IgG-mediated immunity eliminates the organism after invasion.

  Intradermal vaccination of some vaccines, e.g. IPV or Rabies vaccines, can induce antibody responses comparable to intramuscular or subcutaneous route with lesser dose of antigen.
- **Presence of pre-formed antibodies** after immunoglobulin therapy or after blood transfusions interferes with development of adequate immune response by rapid elimination of vaccine-antigen. Hence, a gap of many weeks to months is usually recommended between administration of these products and vaccines. However, as immunological protection by vaccines is delayed by several days. Some immunoglobulins, e.g. tetanus, hepatitis B and rabies immunoglobulins are given along with the first dose of vaccine due to the urgency of protection before appearance of vaccine-induced response.
- ***Contact immunity and herd effect:*** Some vaccines benefit even the unvaccinated population, through various ways, i.e. *Contact immunity* (shedding of the OPV virus in stools or influenza virus in nasal secretions after respective vaccinations, unintentionally vaccinating the contacts) and *Herd effect* (reducing the transmission of disease by decreasing the number of susceptible population). In these cases, the actual protective efficacy of the vaccine might be higher than that expected from the vaccine.

9.1.3 IMMUNIZATION AGENTS

Immunological agents include products for both – active immunization, i.e. vaccines, and passive immunization, i.e. immunoglobulins (discussed later).

TABLE 9.1: Common types of vaccines

I. Live attenuated vaccines	
– Bacterial	BCG, Typhoid
– Viral	OPV, RV, MR/MMR, Varicella, JE, Yellow Fever
II. Inactivated vaccines	
– Bacterial	Pertussis (Whole cell), Cholera, Typhoid
– Viral	IPV, HAV, HBV, HPV, JE (Inactivated), Influenza, ARV
III. Toxoids	Diphtheria, Tetanus
IV. Subunit vaccines	
– Protein	Pertussis (acellular)
– Polysaccharride	PPSV, MPSV, TPSV
– Conjugated	Hib, TCV, PCV, MCV

OPV: Oral polio vaccine; **RV:** Rotavirus vaccine; **MR:** Measles-Rubella; **MMR:** Measles, Mumps, Rubella vaccine; **IPV:** Inactivated polio vaccine; **HBV:** Hepatitis B vaccine; **HAV:** Hepatitis A vaccine; **HPV:** Human papilloma virus vaccine; **JE:** Japanese encephalitis vaccine; **Hib:** *H. influenzae* B vaccine; **PPSV:** Pneumococcal polysaccharide vaccine; **MPSV:** Meningococcal polysaccharide vaccine; **TPSV:** Typhoid polysaccharide vaccine; **TCV:** Typhoid conjugate vaccine; **PCV:** Pnuemococcal conjugate vaccine; **MCV:** Meningococcal conjugate vaccine

Vaccines are biological formulations containing live or killed pathogens, their subunits or their toxins, minus their virulence. Currently available vaccines may be classified, based on the viability of organisms, contents and the methods of production **(Table 9.1)**.

Some commonly used terms in vaccine technology are as follows:

Live vaccines contain viable organisms with attenuated virulence and hence: (a) are highly immunogenic, (b) require stringent storage conditions to maintain viability of organisms, and (c) cannot be used in severely immunocompromised persons due to risk of severe/disseminated disease. These vaccines are usually supplied in lyophilized form to increase their stability and have to be reconstituted before use.

Killed or inactivated vaccines are prepared from organisms inactivated by heat or chemicals to remove the virulence. These vaccines are: (a) less immunogenic and usually need multiple doses for adequate immune response, (b) relatively heat-stable on storage, and (c) can be used in immunocompromised children.

Polysaccharide vaccines using a polysaccharide antigen from cell wall or capsule, are poorly immunogenic due to lack of development of IgG response and memory cells. These vaccines are usually ineffective in younger children before 2 years of age and need re-vaccinations.

Conjugated vaccines are modified polysaccharide vaccines in which component polysaccharides are conjugated with some other potent antigen, termed *vehicle*, (e.g. mutant diphtheria or tetanus toxoid), to increase the immunogenicity. Conjugated vaccines can be used in children < 2 years of age and provide long-lasting immunity.

Polyvalent vaccines are the vaccines with two or more strains of the *same* organism, e.g. OPV, PCV HPV, etc. while monovalent vaccines are single antigen vaccines, e.g. varicella vaccine.

Combination vaccines are vaccines containing antigenic material from *different* organisms, e.g. DPT, MMR and others. These vaccines are useful to minimize the hospital visits, cost and number of pricks.

In addition to the basic antigenic material, vaccines may also contain other agents, collectively termed as excipients and include adjuvants, preservatives, stabilizers and diluents.

Adjuvants, e.g. *aluminium hydroxide or phosphate*, etc., are usually added in inactivated or sub-unit to augment the potency of vaccines to prolong the release of antigen and the attraction of immunocompetent cells around the injection site. Nearly all bacterial vaccines contain adjuvants while viral vaccines are usually adjuvant free, barring few exceptions.

Preservatives, e.g. *mercurial compounds* or *antibiotics*, e.g. neomycin, are added to prevent contamination of vaccines. These agents have been implicated in various adverse events of vaccines, earlier considered due to antigen component. Measles vaccine does not contain any preservative and hence, severe septic reactions, e.g. toxic-shock syndrome have been reported with its use beyond 3 hours of reconstitution.

Stabilizers, e.g. *magnesium chloride*, *sorbitol*, etc. are added to the vaccines to maintain the potency during storage of vaccine and during manufacturing process.

Diluents, e.g. distilled water, normal saline or others are used to reconstitute lyophilized vaccines before use. Only the diluents recommended or supplied by the manufacturers should be used. Some diluents are vaccine specific, e.g. *calcium carbonate* or *citrated sodium bicarbonate* for different RV vaccines.

9.2 INDIVIDUAL VACCINES

Vaccines may be broadly classified as:

- ***Essential vaccines included in National Immunization Schedule,*** i.e. BCG, HBV, OPV, IPV, DPT/Td, RV, PCV, MR and Hib along with Japanese encephalitis (JE) vaccine, which is administered in endemic districts.
- ***Additional vaccines recommended by Indian Academy of Pediatrics (IAP),*** i.e. Hepatitis A, Varicella, Typhoid, HPV and Influenza vaccine.
- ***Vaccines recommended in special circumstances to high-risk children,*** i.e. meningococcal, cholera, rabies, yellow fever and pneumococcal polysaccharide (PPSV) vaccine.
- ***Newer vaccines*** including those under development or not yet available in country, e.g. malaria and dengue vaccines.

9.2.1 VACCINES IN NATIONAL IMMUNIZATION SCHEDULE

NIS in India include routine vaccination of all children with nine vaccines, i.e. BCG, HBV, OPV, IPV, DPT/Td, Hib, RV, PCV and MR, along with additional Japanese encephalitis (JE) vaccine in selected endemic districts. Human papillomavirus vaccine (HPV) is likely to be introduced soon.

BCG vaccine *(bacille Calmette-Guérin vaccine)* is the oldest amongst currently used vaccines (earliest vaccine was smallpox, used in 1798), named after its developing scientists – *Leon Charles Albert Calmette* and *Camille Guérin* (1921).

Contents: It is a *live attenuated vaccine* containing 0.1–0.4 million viable bacilli per dose. In India, *Danish strain* of *Mycobaterium bovis* is used to prepare BCG.

Supply and storage: BCG is supplied as a freeze-dried power in multi-dose, dark-colored vials (light sensitive) and should be reconstituted by mixing with diluents supplied with vaccine or sterile *normal saline* (not with distilled water, which is irritant) just before use. As it is extremely heat and light sensitive, reconstituted vaccine must be used within 3 hours.

Un-open ampoules should be stored in top-most compartment of refrigerator at 2–8°C.

Immunization schedule: BCG is given preferably at birth or the earliest possible opportunity within 48–72 hours of birth (not later than 7 days). *Catch-up immunization* is provided till 1 year in NIS, but recommended up to 5 years by WHO/IAP.

BCG vaccination is not advised in older children due to high likelihood of natural infection but may be given to older children if they are tuberculin-negative, on request.

Dose and administration: BCG is given intradermally over left shoulder as 0.05 ml at birth or 0.1 ml in older infants > 1 month of age. However, WHO recommends 0.05 ml till 1 years of age.

BCG is given with a tuberculin syringe and 26 gauge needle, after cleaning the site with sterile wet swab. Spirit or alcohol swabs as should not be used as it may affect the viability of live vaccine bacilli. On correct administration, vaccine should raise a transient wheal of >5 mm over injection site. SC or IM injected vaccines are rapidly cleared by lymphatics and may not induce desired immune response or may cause local complications.

After vaccination, the wheel disappears after 20–30 minutes and nothing is visible at site, followed by progressive induration after 3–4 weeks, ulceration after 6–8 weeks and scar formation after 10–12 weeks. In some children, the process of ulceration may be repeated 2–3 times, before eventual scarring.

Protective efficacy: Unlike other vaccines, BCG protects by inducing *cell mediated immunity* rather than humoral

immunity. Protective value of BCG is controversial, generally accepted as ~70–90% for severe disease, e.g. miliary or neurotuberculosis and 50–60% against pulmonary tuberculosis.

Successful uptake of BCG vaccine may be judged after 8–12 weeks, by local scar formation, tuberculin conversion or specific tests for cell mediated immunity. However, absence of scar does not necessarily mean absence of cell mediated immunity, which may disappear over time after 5–10 years. If a child fails to develop the scar after 12–16 weeks of vaccination, BCG may be repeated on the opposite side.

Side effects are rare and include:

- *Local reactions* including secondary infection or keloid formation are seen in 1:1000–10000 vaccinees despite correct administration, depending on strain and bacillary load in the vaccine. Danish strain used in India is more reactogenic.
- *Regional* lymphadenitis after ~4–8 weeks is not uncommon due to lymphatic spread of viable bacilli and no treatment is required except reassurance. It regresses spontaneously in next few weeks or months. However, suppurative lesions need antibiotics. Surgical drainage should be avoided to prevent sinus formation though very large nodes may be removed after completion of antibiotics, if required. Antitubercular therapy is not required even if FNAC is positive for AFB, which is expected due to presence of bovine bacilli in the vaccine.
- *Disseminated disease (BCGiosis)* is extremely rare (1:1–4 million) but may develop in immunocompromised children.

Contraindications are none, except congenital or acquired immunodeficiency states, e.g. AIDS and steroid/cytotoxic therapy. In *asymptomatic HIV* infected children, BCG vaccination is safe and should be given as a routine, unless they have evidence of severe immunosuppression.

DPT (Triple vaccine) is a combination vaccine against three diseases: Diphtheria, tetanus and pertussis. Depending on the pertussis fraction, this vaccine is termed as DTwP (containing whole cell killed bacilli) used in NIS; and DTaP (containing acellular pertussis antigens). DTaP is not provided in NIS. Another triple vaccine containing low-dose of diphtheria toxoid with acellular pertussis antigens (Tdap) is also available for use in older children > 7 years but not in NIS.

Other related vaccines without pertussis component include DT, Td (Low-dose diphtheria for use in older children ≥10 years and mono-antigenic tetanus toxoid.

DTwP and DTaP vaccines are also available as combination vaccines with HBV and Hib (pentavalent), some also containing IPV (Hexavalent).

Contents: DTwP contains diphtheria toxoid (25 Lf) tetanus toxoid (5 Lf) and killed whole cell pertussis bacilli (20,000 million).

Supply and storage: DTwP in NIS is administered as a pentavalent vaccine with HBV and Hib and should be stored in middle compartment of refrigerator (2–8°C).

Dosage and administration: *0.5 ml* of vaccine is given IM over lateral aspect of thigh.

Immunization schedule: In NIS, Primary doses of DPT are given as pentavalent vaccine at 6th, 10th and 14th week of life, followed by two boosters of stand-alone DPT at 15–18 months and 4–5 years.

Catch-up immunization below 7 years include three doses of DTwP at 0,1,6 months with a booster after 6 months of last dose. Second booster is not required if the last primary dose was given after 4 years of age.

DTwP/DTaP vaccines should not be used above 7 years of age for boosters or catch-up immunization (Low-dose diphtheria vaccines, e.g. Td/Tdap are used in them, if required).

Protective value is 100% for diphtheria and tetanus and ~80% for pertussis.

Side-effects are *mainly due to pertussis fraction* and include:

- *Local reactions, e.g.* pain, swelling and tenderness, which may be relieved with cold compresses.
- *Transient fever* for ~24 hours, which may be treated with paracetamol. Occasionally, it may lead to febrile seizures.
- *Rare but serious neurological events*, e.g. inconsolable cry, hypotonic-hyporesponsive episodes, seizures and encephalopathy.

Frequency of local reactions increases and systemic reactions decreases with increasing order of doses.

Inconsolable cry refers to >1 hour of continuous, inconsolable cry within 24 hours of vaccination. It occurs more frequently after the first dose and recurrence is unlikely after subsequent doses.

Hypotonic-hyporesponsive episodes (HHE) refers to sudden onset of limpness, reduced responsiveness and pallor or cyanosis within 48 hours of vaccination, (also reported with PCV vaccine). Recovery is spontaneous with no sequelae. Further doses may be given safely without recurrence.

Contraindications include:

- History of anaphylaxis or encephalopathy with previous dose.
- Progressive neurological disease

No pertussis-containing vaccines (not even DTaP) should be given as further dose in these cases (use DT). Cases with other neurological events may be given

further doses, if required, under caution and longer observation period, preferably in the hospital.

DTaP vaccines, instead of whole cell bacilli, contain two or more of the following five separately purified pertussis antigens—*pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbrial hemagglutinins 1,2 and 3 (FIM type 2 and 3)*. It is also available in combination as pentavalent or hexavalent vaccine.

Not used in NIS, DTaP can be used with similar dose schedule and have lower incidence of local pain and fever following vaccination. While DTwP vaccines are marginally more immunogenic, IAP recommends use of DTaP as a substitute of DTwP for primary as well as booster doses. DTaP may also be preferred to DTwP in children for booster doses due to lower reactogenicity and in those with history of severe adverse effects after previous dose of DTwP. It should be noted that serious side-effects, e.g. anaphylaxis and encephalopathy may develop even after DTaP, which should not be used for further doses after history of such events to previous dose of DTwP/DTaP .

Tdap vaccine, contains lower dose of diphtheria toxoid (2.5 Lf instead of 25 Lf). While not included in NIS, IAP recommends single dose of Tdap for:

- All fully immunized adolescents at 11–12 years,
- All pregnant women at 27–36 weeks irrespective of previous doses,
- Catch-up immunization in fully/partially unimmunized children older than 7 years as the first dose, followed by subsequent Td dose/s, if required.

Catch-up immunization is advised till 18 years and more than one dose of Tdap is not recommended except in pregnancy.

Td, a bivalent vaccine containing low dose of lower dose of diphtheria toxoid (Diphtheria toxoid 2 Lf) has ***replaced TT*** in NIS for (a) Booster doses in children at 10 and 16 years, and (b) Two doses 4 weeks apart in early pregnancy, (single dose, if last pregnancy dose received within 3 years)

IAP also recommends Td as: (a) subsequent dose for catch-up immunization after first dose as Tdap, (b) booster doses to fully immunized children every 10 years, and (c) instead of TT for wound care.

DT (Diphtheria toxoid 25 Lf, Tetanus toxoid 5 Lf), is no longer recommended except in rare instances when pertussis containing vaccine is contraindicated in children < 7 years.

TT (Tetanus toxoid 5 Lf) has been replaced by Td for all indications, except for wound care in some circumstances.

Polio vaccine: Two types of polio vaccines are available—a live, oral, ***Sabin vaccine (OPV)*** and an inactivated, parenteral ***Salk vaccine (IPV),*** named after their developers, each with its advantages and disadvantages.

After the elimination of poliomyelitis from the country, India is gradually and cautiously shifting from OPV to IPV to minimize the risk of vaccine-induced poliomyelitis, more common with OPV. However, only IPV schedule is not yet advisable due to risk of importing wild virus from endemic countries and OPV providing better local gut immunity than IPV.

Both OPV and IPV vaccines are used in NIS as well as in IAP recommended schedule, though with some differences.

Contents: OPV is a *live attenuated, bivalent* vaccine, containing only serotypes-I and III, while IPV is an inactivated trivalent vaccine containing serotypes I, II, III.

India has removed type II serotype from OPV since 2016, after it was declared eradicated globally in 2015. (Now type III has also been declared globally eradicated since 2019, and all cases of poliomyelitis at present are due to type I only).

Supply and storage: OPV is supplied as multi-dose vials with dropper. It is *extremely heat-sensitive* and maintenance of adequate cold chain is extremely vital. It should be stored at-20°C in large depots, in the freezer at clinic level and must reach immunization center at 2–8°C in vaccine carriers.

Each OPV vial is marked with *vaccine vial monitor*, i.e. a sticker with a lighter square inside a darker circle (see **Fig 9.5**). *If the color of square is darker or matching the outer circle, vaccine is probably not potent and should not be used.*

IPV is supplied as a multi-dose vial in NIS and as a single dose vial/prefilled syringe outside the program. Single dose IPV is usually in short supply as a stand-alone vaccine, but available as commercial combination vaccines with DTwP/DTaP + HBV and Hib vaccines. IPV should be stored in middle compartment of refrigerator at 2–8°C.

Dosage and administration: OPV is given as 2 drops orally while IPV is given either as: (a) Fractionated dose of 0.1 ml intradermally in NIS ($_f$IPV), or (b) Regular dose of 0.5 ml IM/SC in private set-up (usually as combination vaccine).

Immunization schedule: In NIS, total five doses of OPV are recommended - at birth (*zero dose*), three primary doses at 6–10–14 weeks and a single booster at 16–24 months; along with three doses of fractionated IPV at 6, 14 weeks and 9 months. Additional OPV doses given during pulse polio campaign should not be counted in routine immunization.

IAP recommends only single dose (zero dose) of OPV at birth; followed by five doses of IPV including three primary doses at 6–10–14 weeks and two booster doses at 4–6 years.

Protective efficacy: OPV mainly provides local mucosal immunity by engaging receptor sites in the gut with

TABLE 9.2: Common Vaccines at a glance

Vaccine	*Type*	*Dose*	*Schedule*	*Protective efficacy*	*Adverse events*	*Contraindications*
BCG	Live	ID 0.05 ml[1]	At birth	50-60%[2]	BCG adenitis	Immunodeficiency
OPV	Live	PO 2 drops	*NIS:* 0, 6,10,14 wk, 16-24 mo (B) *IAP:* Zero dose only (at birth)	65-70%	VAPP/ VDPV	–
IPV	Inactivated	ID 0.1 ml IM/SC 0.5 ml	*NIS (ID):* 6, 10 wk, 9 mo *IAP (IM):* 6,10,14 wk, 16-18 mo (B1), 4-6 yr (B2)	>85%	Local, AFI-	–
DTwP/ DTaP	Toxoids/ Inactivated	IM 0.5 ml	*NIS:* (DTwP) 6,10,14 wk, 16-24 mo (B1), 5-6 yr (B2) *IAP:* (DTwP/DTaP) 6,10,14 wk, 16-18 mo (B1) 4-6 yr (B2)	100% for DT 80% for P	Local, AFI, HHE, seizures Encephalopathy	Progressive CNS disease, Anaphyalxis/ Encephalopathy with previous dose
HBV	Subunit	IM 0.5 ml	*NIS:* 0,6,10,14 wk *IAP:* 0,6,10,14 wk (or 6 mo)	>95%	Very rare	–
Hib	Conjugated	IM 0.5 ml	*NIS:* 6,10,14 wk *IAP:* 6,10,14 wk, 16-18 mo(B)	95–100%	Local, AFI	–
RV	Live	PO 5 drops[3]	*NIS/IAP*: 6,10,14 wk	50-60%	Intussusception	H/o Intussusception with previous dose
PCV	Conjugated	IM 0.5 ml	*NIS:* 6,14 wk, 9 mo *IAP:* 6,10,14 wk, 15 mo(B)	>80-90%	Local, AFI, HHE	AFI, HHE, seizures
MR/MMR	Live	IM/SC 0.5 ml	*NIS* (MR): 9-12 mo, 16-24 mo *IAP*: (MMR) 9 mo, 15 mo, 4-6 yr	M: >95% R: >99% Mumps>90%	Rash, TCP, SSPE	Immunodeficiency, untreated TB
JE	Inactivated	IM/SC 0.5 ml	*NIS:* 9-12 mo, 16-24 mo (in endemic districts only) *IAP:* 0,6 mo after 1 yr of age	90%	Local, AFI	AFI ?
Influenza*	Subunit	IM/SC 0.5 ml	6 mo, 7 mo > annually till 5 yr	55-60%	Local, febrile seizures, GBS	Egg allergy, H/O GBS
HAV*	Inactivated/ Live	IM 0.5 ml	Inactivated: 12 mo, 18-19 mo *Live:* Single dose at 12 mo	90-95%	Local, AFI	None
TCV*	Conjugated	IM/SC 0.5 ml	Single dose 6-9 mo	>98%		None
Varicella*	Live	SC 0.5 ml	15-18 mo, then after 3-6 mo	98%	MVLI, VCZ	Immunodeficiency, salicylate therapy
HPV*	Inactivated	IM 0.5 ml	Age 9-14 yrs: Two doses at 0,6 mo Age >14 yrs: Three doses at 0,1/2, 6 mo	90%		None

Starred (*) vaccines are not included in NIS at present.
Figures in parentheses after NIS/IAP denote total number of doses, required to complete immunization
[1]0.1 ml after 1 mo of age, [2]Over 80-90% for Neuro/Miliary TB, [3]Doses of commercial preparations vary from 2.5-5 ml,
AFI: Acute febrile illness; **B:** Booster; **GBS:** Guillain-Barré syndrome; **HHE:** Hypotonic, hyporesponsive episodes; **MVLI:** Modified varicella like illness; **SSPE:** Sub-acute sclerosing panencephalitis; **TCP:** Thrombocytopenia; **VCZ:** varicella zoster

vaccinia virus, thus preventing attachment of wild virus strains. While it is a highly potent live vaccine, both serotypes may not be taken up during each dose. Consequently, efficacy of the vaccine increases with increasing number of doses.

Protective efficacy of OPV is relatively less in developing counties like India (~65–70% after 3 doses) than in developed countries (~100%), perhaps due to interference with maternal antibodies and frequent presence of enteric infections preventing uptake of the vaccine.

OPV also provides herd immunity, even in unimmunized population due to excretion of vaccine virus in stools for variable period, which can infect the contacts to provide immunization.

IPV predominantly provides systemic immunity with seroconversion rate of >85% after three intramuscular doses. Fractionated interdermal doses are almost equally immunogenic at lower cost.

Side-effects: IPV is very safe except minor local reactions in some cases, while OPV carries potential but very rare risk of causing vaccine-related disease, as follows:

Vaccine associated paralytic polio (VAPP) is an extreme rare complication (1 per 2–4 million doses), more common with the first dose and in developed countries. In India, VAPP risk is lower, perhaps due to presence of maternal antibodies, birth dose of OPV and lower "*take-up*" of the vaccine. Defined as *acute flaccid paralysis with residual weakness for 60 days after the onset with isolation of vaccine virus in stools* (not wild virus), VAPP is caused by loss of attenuating mutations and reversion to neurovirulence during replication of the vaccine virus in the gut. VAPP may develop in the vaccine recipient (within 4–40 days of receiving OPV (*recipient VAPP*) or in contacts of the recipients, who is shedding of virus in stools (*Contact VAPP*).

Vaccine derived polioviruses (VDPV) denotes mutation of parent vaccine virus and recombination in the human gut with 1–15% divergence. These modified viruses are not only neurovirulent, but also transmissible and capable of causing outbreaks. VDPV are also classified as–cVDPV with evidence of virus circulation in the population, *iVDPV* in the immunodeficient person and *aVDPV* of ambiguous origin isolated from environmental sources without evidence of circulation. VDPV is more common following vaccination of immunodeficient children. Almost 90% of VDPV cases were due to Type II serotype, which has now been removed from the vaccine.

Possibility of VAPP/VDPV should be considered in any cases of acute flaccid paralysis with: (a) OPV vaccination in preceding 30 days, (b) contact with recently immunized child in preceding 60 days, or (c) pulse polio campaign in the community in preceding 60 days.

Contraindications are none, except for OPV in severe immunodeficiency states due to potential risk of VDPV in them or contacts. IPV may be safely used in these cases.

Measles containing vaccines (MCV) are combination vaccines including MR (Measles and Rubella) and MMR (Measles, Mumps and Rubella). Stand-alone measles vaccine has been withdrawn from India since 2018. Another combination vaccine of MMR with varicella (MMRV) is also available commercially. In NIS, only MR is used, though some states/cities provide one dose of MMR instead of second dose of MR at 16–24 months from their own resources.

Contents: All MCVs are live attenuated vaccines, containing *Edmonston-Zagreb* or *Schwarz* strain, containing of measles virus and *Wister RA/3M strain of rubella virus* (MR), *with or without Urabe Am 9* strain of Mumps virus (in MMR).

Supply and storage: Both MR and MMR vaccines are available as single dose or multi-dose vial containing lyophilized powder along with diluent and should be reconstituted before injection.

All MCV Vaccines should be stored at 2–8°C and once reconstituted, should be used within *6 hour*. Severe reactions, e.g. *toxic-shock syndrome* have been reported after delayed use of contaminated vaccine, which does not contain anti-bacterial preservative.

Dosage and administration: 0.5 ml IM or SC over anterolateral aspect of thigh for both MR and MMR vaccines.

Immunization schedule: IN **NIS**, two doses of MR vaccine are recommended at 9–12 months and 16–24 months, while **IAP** recommends use of MMR instead of MR with three doses at 9 months, 15 months and 4–6 years.

MCVs are not recommended before 9 months due to potential interference with maternal antibodies, though it may be given as early as 6 months during outbreaks. However any baby, who has received MCV before 9 months, should receive additional dose at 9 months to ensure adequate seroconversion. No boosters are needed, as single dose confers life-long immunity.

For catch-up immunization after 1 year of age, two doses of MMR are recommended with minimum four weeks interval. In adolescent girls, pregnancy should be excluded due to risk of congenital rubella syndrome.

Protective efficacy: Seroconversion rate for measles in 80–85% if given at 9 months and >95%, if given after 12 months of age. Seroconversion rate for rubella is even better >95% and >99% when given before or after 12 months respectively.

Almost all children vaccinated with MR after 12 months do not required second dose. However, high epidemiological risk of measles in infants aged 9–12 months in India has necessitated to provide MR vaccine as early as possible, i.e. at 9 months, followed by second dose after 12 months to ensure adequate protection.

Seroconversion rate for mumps-component following MMR vaccination is also good at ~90%, though antibody titers decline with time and third dose of MMR is recommended by IAP at 4–6 years to ensure by IAP, to ensure life-long protection against mumps.

Side effects: All MCVs are very safe, except mild local reactions, transient morbilliform rash after a week in 2–5% cases and transient thrombocytopenia as well as immunosuppression, which are often asymptomatic.

However, maximum number of immunization-related deaths are reported with MR/MMR due to inadequate aseptic precautions and bacterial contamination of the vial due to use beyond 4–6 hours.

Sub-acute sclerosing panencephalitis or SSPE (Ch 18.15) has been very rarely reported (< 1 per million doses) following MCV vaccinations.

Contraindications include (a) severe immunodeficiency states as these are live vaccines, (b) pregnancy due to potential risk of congenital rubella syndrome and (c) active untreated tuberculosis, as MCVs induce transient immunosuppression, which may fare-up the disease. MCV vaccinations should be deferred till antitubercular therapy has been given for 4–6 weeks.

Hepatitis B vaccine (HBV): Currently available HBV are recombinant vaccines, available as stand-alone vaccines or as combination vaccine with DPT, DPT+Hib, DPT+Hib+IPV or HAV.

Contents: HBV contains a suspension of alum-adsorbed recombinant HbsAg particles as 20 µg/ml.

Supply and storage: HBV is available as single or multi-dose ready-use vials with pediatric and adult dose formulations. In NIS, it is provided as pentavalent vaccine with DTwP and Hib.

Dosage and administration: HBV in children is given as 0.5 ml IM over anterolateral aspect of thigh. A higher dose of 1.0 ml is required for adults > 18 years of age.

Immunization schedule: In **NIS**, four doses of HBV are given, first dose within 24 hours of birth as stand-alone HBV (*Birth dose*) and subsequently 3 primary doses at 6–10–14 weeks as pentavalent vaccine with DTwP and Hib. IAP recommends similar schedule, but with last dose at 6 months of age rather than at 14 weeks.

Immunological response to HBV may be poor in preterms and LBW < 2000 gm, in whom the birth dose may be deferred till chronological age of one month (provided mother is HBsAg negative) or alternatively, the birth dose is given but not counted.

Infants born to HbsAg positive mothers should also receive HBIG (IM 0.5 ml) within 24 hours of birth along with HBV at a different site (Ch 15.4).

While three doses are enough to complete HBV immunization, birth dose is given additionally in routine immunization to ensure some protection to newborns of HBV positive mothers.

For catch-up immunization, only three dose schedule of HBV at 0, 1 and 6 months is recommended.

No booster is required, except in immunocompromised or occupationally exposed persons, in who antibody titers drop below the protective level over time (<10 mIU/ml) and booster dose may be needed after estimation of antibody titers.

Protective value: Seroconversion rate after 3 doses is >95%, with immunity lasing for >20 years. While antibody titers may decline with time, periodic testing is recommended only in children of HBsAg positive mothers, health workers and those with co-morbidities.

Side-effects are very rare, except local pain/erythema and transient fever in some cases.

Contraindications are none, except in rare instances of serious allergic reactions to previous dose.

***H. influenzae* B (Hib) vaccine:** Hib vaccine is available a stand-alone vaccine or as a combination vaccine with DPT, DPT+HBV, DPT+HBV+IPV, etc.

Contents: Hib vaccines are conjugated vaccines, containing a purified polysaccharide component of the organism, conjugated with a carrier protein to boost immunogenicity. Depending on the carrier protein, three Hib vaccines are available—HbOC (carrier mutant *C. diphtheria* toxin protein), PRP-T (carrier tetanus toxoid) and PRO-OMP (carrier *N. meningitidis* protein outer membrane protein complex), though last one is not available in India.

Supply and storage: Stand-alone Hib vaccines are lyophilized vaccines, supplied as single-dose (10 µg/0.5 ml) vials with diluent, to be reconstituted just before the use and should be stored at 2–8°C. However stand-alone Hib vaccines are not freely available in India at present and combination vaccines have to used.

Dosage and administration: 0.5 ml IM or SC, after reconstitution.

Immunization schedule for Hib varies with age, requiring three primary doses at 6, 10, 14 weeks followed by a booster at 12–18 months in infants <6 months, two primary doses at 0,1 month with a booster at 12–18 months in infants aged 6–12 months, and one primary dose and one booster after 8 weeks in children aged 12–15 months. Only single dose is required after 15 months of age, without any booster.

Vaccination beyond 5 years is not justified due to rarity of Hib infection, except in high-risk children, e.g. those with asplenia, splenectomy, sickle cell disease, etc. (Ch 9.4).

However in *NIS*, Hib is given as pentavalent vaccine at 6–10–14 weeks without any booster, while *IAP schedule* recommends one booster at 16–18 months, usually with DPT and IPV as combination vaccine.

Protective value: 95–100% for one year against culture proven invasive Hib disease. Hib vaccination also provides *herd protection* by reducing nasopharyngeal carriage of organisms.

Side effects are uncommon except mild fever and local reaction.

Contraindications: None, though dose should be deferred during acute severe febrile illness.

Rotavirus (RV) vaccine: Despite the high morbidity and availability of suitable vaccines, RV immunization was not widely used till recently due to potential fear of intussusception with older vaccines. With new generation RV vaccines, this risk has been minimized to acceptable limits and NIS has included RV in universal immunization program since 2016.

Contents: Currently, four RV vaccines are available in India-human monovalent vaccine (RV_1), human-bovine pentavalent vaccine (RV_5), human-bovine monovalent vaccine ($RHBV_1$) and bovine-human reassortant pentavalent vaccine (BRV-PV). $RHBV_1$ has been developed from a strain derived from Indian newborns and is being used in NIS, though all vaccines are equally effective and safe.

Supply and storage: $RHBV_1$ and RV_5 are liquid ready-to-use vaccine, while RV_1 and BRV-PV are lyophilized vaccines to be reconstituted before use with given diluents. All RV vaccines must be stored at 2–8°C and not be frozen.

Dosage and administration: All RV vaccines are given orally but in different doses – 0.5 ml $RHBV_1$, 1.0 ml RV_1, 2 ml RV_5 or 2.5 ml BRV-PV. *However, in NIS, a different $RHBV_1$ formulation is used, given as only 5 drops orally.*

Immunization schedule in *NIS,* three doses of $RHBV_1$ vaccine is given at 6,10 and 14 weeks with catch-up immunization at one month interval till 1 year of age (though $2^{nd}/3^{rd}$ dose/s may be given later, if the first dose was given before 1 year of age). WHO recommends RV vaccination till 2 years of age.

IAP also supports similar schedule at 6–10–14 weeks (only two doses at monthly interval are required for RV_1). However, it recommends that RV vaccination should be not be initiated after 15 weeks of age due to safety concerns and all doses should be completed by 32 weeks.

Protective value: All RV vaccines are equally immunogenic and protective, with reported efficacy of ~50–60% against severe RV gastroenteritis (SRVGE), for at least two years. Protective efficacy is lower in developing countries than in developed countries (~80–90%), due to interference by maternal antibodies, widely prevalent malnutrition and co-infection with other enteric pathogens.

Side-effects are none except a definite but very small risk of acute intussusception (~1–2/lac vaccines), specially after the first dose. However, benefits of vaccination to prevent SRVGE outweigh this miniscule risk.

Contraindications are none, except past history of intussusceptions. Vaccine can be co-administered with OPV.

Pneumococcal conjugate vaccine (PCV): Two types of pneumococcal vaccines are available—conjugate vaccine (PCV) for routine immunization and polysaccharide vaccine (PPSV), as an additional vaccine for high-risk children. PCV has been included in NIS since 2017. Following information pertains to PCV vaccines.

Contents: Currently three PCV vaccines are marketed in India, containing 10, 13 and 14 pneumococcal antigens. PCV_{10} is used in NIS. However, PCV with more than 14 serotypes are also in pipeline.

Supply and storage: All PCV vaccines are available as ready-to-use suspension in vials/prefilled syringes, which must be stored at 2–8°C and not be frozen.

Dosage and administration: 0.5 ml/dose IM for all vaccines.

Immunization schedule varies with age, requiring three primary doses at 6,10,14 weeks followed by a booster at 12–15 months in infants <6 months, two primary doses at 4 weeks interval with a booster in second year in infants aged 6–12 months, and two doses at 8 weeks interval after infancy. PCV_{13} needs only single dose after 2 years of age.

However in ***NIS***, total three doses of PCV_{10} are given as two primary doses at 6 and 14 weeks and a booster at 9 months with catch-up immunization till 1 year of age.

IAP recommends total 4 doses for routine immunization at 6, 10, 14 weeks and booster at 12–15 months, with catch-up immunization till 5 years of age, using manufacturers' recommended schedule.

PCV_{13} is also licensed for use as a single dose in older children 6–17 years and adults >50 years.

Protective value: All PCVs are equally immunogenic with >90% seroprotection following primary doses. However, protective efficacy depends on the number of serotypes included in the vaccine and number of doses. PCV 10 and 13 cover ~70% and ~80% of serotypes respectively, with protective efficacy of ~48%, ~87% and ~100% after 1, 2 or 3 doses respectively.

In general, protective efficacy of PCV is estimated to be ~80% against invasive pneumococcal disease due to vaccine serotypes and ~60% against all cases irrespective of serotypes, provided all primary doses are given before 6 months of age. Protective value is relatively less (~25–35%) against pneumococcal pneumonia or otitis media.

Side effects are rare and comparable with both vaccines, except local reactions and mild fever. Hypersensitivity,

seizures and hypotonic-hyporesponsive episodes have been rarely reported.

Despite excellent efficacy of PCV vaccines, a major concern is the ***Serotype replacement disease,*** i.e. causation of disease due to serotypes not including in the vaccine, thus offsetting the benefits of immunization. Surveillance programs have documented this phenomena in countries with high immunization coverage, despite substantial reduction in invasive pneumococcal disease.

Contraindications are none except severe allergy to previous dose or carrier protein, e.g. diphtheria toxoid.

Pneumococcal polysaccharide vaccine (PPSV) is an unconjugated polysaccharide vaccine containing 23 serotypes, responsible for >80% cases of serious disease. However, it is poorly immunogenic in children <2 years and does not reduce nasopharyngeal carrier state. It is given as single dose (0.5 ml SC/IM), *only* to high-risk children, i.e. those with chronic lung/heart disease, CSF leakage, cochlear implant, anatomical/functional asplenia, sickle cell disease and immunodeficiency. Revaccination is required after 3 years, but more than two doses are not recommended due to immunological hyporesponsiveness.

IAP does *not* recommend use of PPSV alone in these cases, who should receive PPSV only after completing age-related PCV immunization, at least 8 weeks after the last PCV dose. High-risk children, even if already vaccinated with PPSV, should receive recommended PCV doses.

Japanese encephalitis vaccine: Government of India has identified ~268 endemic districts for JE, where this vaccine is included in NIS. IAP recommends it only to—(a) children residing in endemic regions and (b) travellers to these regions, staying for >4 weeks.

Contents: Currently, three JE vaccines are licensed in India—one *live attenuated vaccine* derived from SA14–14–2 strain and two *inactivated vero-cell derived vaccines* from different strains, i.e. SA14–14–2 strain and 825146XY strain from Kolar, India. Of these, only live attenuated vaccine is used in NIS, though others are commercially available.

Supply and storage: Live JE vaccine is a lyophilized vaccine, to be reconstituted before use. Both inactivated vaccines are liquid suspensions. All vaccines must be stored at 2–8°C, though live vaccine is heat-stable at 37°C for 7–10 days.

Dosage and administration: Live vaccine is given as 0.5 ml SC over left upper arm (Right upper arm is used for MR vaccination during same visit), while inactivated vaccines are given as 0.5 ml IM (0.25 ml for SA14–14–2 vaccine in children <3 years).

Immunization schedule: under *NIS*, two doses of live JE vaccine are given at 9–12 months and 16–24 months, with catch-up immunization till 15 years of age (or even more in some states).

IAP recommends two doses of inactivated vaccines at one month interval after one year of age with catch-up immunization till 18 years of age.

Protective efficacy: Efficacy of live vaccine is ~90% with two doses and > 90% with both inactivated vaccines, though titers may decline gradually.

Side effects: All JE vaccines are equally safe except transient fever and local reactions in few cases.

Contraindications are none, though vaccination should be avoided during acute febrile illness.

9.2.2 ADDITIONAL VACCINES RECOMMENDED BY IAP

In addition to vaccines discussed earlier, IAP also recommends some other vaccines, which are desirable in all children but current logistics preclude their inclusion in the NIS and have to be purchased by parents. While *often termed as optional, these vaccines are of no less importance and should be offered to all children* after one to one discussion with parents. Some of these vaccines are being gradually introduced in NIS.

Human papillomavirus (HPV) vaccines: HPV is the commonest sexually transmitted infection in adolescents and adults, associated with development of genital warts and cervical, anogenital and oropharyngeal cancers in later life. High-risk serotypes 16 and 18 cause ~70% cases of cervical cancers.

India plans to introduce HPV vaccine soon in NIS, using an indigenously developed vaccine.

Contents: All HPV vaccines are recombinant vaccines differing in the number of serotypes. Currently, three types of HPV vaccines are available—a *bivalent* vaccine (HPV_2) containing serotypes 16 and 18, a quadrivalent vaccine (HPV_4) containing four serotypes 6, 11, 16 and 18 and a nonavalent vaccine (HPV_9) containing nine serotypes. First indigenous HPV_4 vaccine has also been launched in 2023, expected to be used in NIS.

Supply and storage: All HPV vaccines are single dose 0.5 ml ready-to-use suspension, which must be stored at 2–8°C and not be frozen.

Dosage and administration: 0.5 ml/dose IM for all HPV vaccines.

Immunization schedule: In India, HPV vaccines are licensed for use only in females from 9 years to 26 years of age, with 3 doses at 0, 1, 6 months (for HPV_2) or 0, 2, 6 months (for HPV_4 and $_9$).

However, IAP recommends 2-dose schedule at 0, 6 months in girls < 15 years, which is equally immunogenic. For older or immunocompromized girls, standard 3-dose schedule is recommended.

NIS plans to introduce indigenous HPV_4 in two-dose schedule for girls aged 9–14 years.

IAP also recommends two doses of HPV_9 or Indigenous HPV_4 at six month interval to all boys aged 9–14 years to prevent genital warts and anogenital cancers (not beyond 14 years).

Protective value: All vaccines are equally immunogenic with ~90% protection against HPV infection/disease due to vaccine serotypes in females, not infected till the time of vaccination. Pre-adolescent immunization is superior to the immunization in older females as the vaccine does not alter outcome of HPV16/18 infection already acquired before vaccination.

Side-effects are rare except mild fever and local reactions. Syncopal attacks are common in adolescent girls, who must be observed for 30 minutes after vaccination.

Contraindications are none except allergic reaction to previous dose and should be avoided during pregnancy.

Typhoid vaccine: In India, two types of typhoid vaccines are available, both active against Vi-capsular polysaccharide antigen: (a) polysaccharide vaccine (TPSV), and (b) conjugate vaccine (TCV), using a carrier protein, e.g. tetanus or diphtheria toxoid to boost its immunogenicity.

Contents: All TPSVs contains 25 µg/dose of capsular Vi antigens, while antigenic dose in TCV varies 5 to 25 µg/dose.

Supply and storage: All vaccines are supplied as single dose vials, to be stored at 2–8°C.

Dosage and administration: All vaccines are given as 0.5 ml/dose IM or deep SC.

Immunization schedule: *Not included in NIS*, IAP recommends a single dose of TCV to all children at 6–9 months of age, with catch-up immunization up to 18 years.

TPSV is no longer preferred due to poor immunogenicity of polysaccharide vaccines in children < 2 years and need for revaccination every 3–5 years.

Protective value of TCV is >98% after 42 days of vaccination. While antibody titers decline with time, all vaccinees are protected for 3–5 years and then, the immunity is expected to be further boosted due to subclinical natural infections.

Despite the high seroconversion rate of >98% after TPSV vaccination, protective efficacy is only 55–70% for 2–3 years.

Side-effects are rare, except local pain and erythema. Vaccines do not interfere with widal test reports.

Contraindications: None, except past history of allergy.

Hepatitis A vaccine (HAV): While recommended by the IAP to all children, HAV vaccine is particularly important in high-risk children, e.g. those with chronic liver disease, hepatitis B/C carriers, immunodeficiency states, transplant recipients, institutionalized children and travelers to endemic regions. HAV vaccine can also be used for post-exposure prophylaxis in household contacts of a case, when given within 10 days.

Contents: Two types of HAV vaccines are available in India—*inactivated vaccines* derived from HM 175/GBM or RG-SB strain and a *live attenuated vaccine* derived from the H2 strain. It is also available as a combination vaccine with HBV.

Supply and storage: Inactivated vaccines are liquid and ready to use, available in different formulations for children (0.5 ml) and adults (1.0 ml). Live attenuated vaccine is a freeze-dried vaccine, to be reconstituted before use. All vaccines need to be stored at 2–8°C.

Dosage and administration: *Inactivated vaccines* are given IM as 0.5 ml in children and 1.0 ml in adults >19 years. *Live attenuated vaccine* is given as 0.5 ml SC.

Schedule: Not included in NIS, IAP recommends either two dose of inactivated HAV 6–18 months apart during 12 to 23 months of age *or* only a single dose of live vaccine at 12 months age. Catch-up immunization is recommended till 10 years.

For catch-up vaccination in older children/adolescents >10 years, IAP recommends pre-vaccination screening for HAV antibodies due to substantial chance of natural infection and immunity by this age.

Combined HAV+HBV vaccine needs three doses at 0, 1, and 6 months.

Protective value is >90–95% for at least 10 years with both vaccines, followed by natural boosting. Single dose of inactivated or live HAV may also be used as post-exposure prophylaxis.

Side effects are uncommon, except mild fever and local reaction.

Contraindications are none, though dose should be deferred during acute severe febrile illness.

Varicella vaccine: IAP recommends varicella vaccine to all children without previous disease, with special emphasis in high-risk children, e.g. those with chronic lung/heart disease, immunocompromised states and institutionalized children attending crèches, day-care centers, or orphanages. It may also be used for post-exposure prophylaxis in contacts of a case, when given within 3 days of exposure.

Contents: It is a live-attenuated vaccine, prepared from *Oka strain* of varicella-zoster virus, with each dose containing minimum 1350 PFU (plaque forming units) organisms.

Supply and storage: It is supplied as a single-dose lyophilized powder with diluent, which should be stored at 2–8°C.

Dosage and administration: 0.5 ml subcutaneously (not IM).

Immunization schedule: IAP recommends two doses – first at 15–18 months and second after 3–6 months of the first dose. High-risk children may be given two doses at shorter interval of 8 weeks.

Catch-up immunization is recommended till 18 years with two doses at 8–12 weeks interval.

Protective value is ~85–90% with one dose and >98% with two doses, better for moderate to severe disease than mild disease. Varicella vaccine is also known to reduce the incidence of herpes zoster by ~50% in adults.

Side-effects are mild and transient, including local reactions. Some children may develop transient and mild papulovesicular eruptions after 1–3 weeks, termed as *modified varicella like illness or MVLI*.

Breakthrough varicella, usually with milder disease, has been reported >6 weeks following immunization in 1–4% vaccines, specially those vaccinated <15 months of age or in late childhood.

Herpes zoster is also known to occur with vaccine, but incidence is far less than in unvaccinated children.

Contraindications: Being a live vaccine, it should not be given to severely immunocompromised children or during pregnancy. Salicylates should be avoided for 6 weeks post-vaccination due to potential risk of Reye syndrome.

Influenza vaccines: IAP recommends influenza vaccine to all children annually from 6 months to 5 years of age and to high-risk children beyond this age including those with immunodeficiency states, diabetes or chronic cardiac, pulmonary, hematologic, renal or liver disease.

Contents: All available influenza vaccines in India are trivalent or quadrivalent *inactivated* vaccines (IIV), containing two serotypes A and one or two serotypes B viral strains, recommended by WHO annually, depending on prevalent strains in previous season. All vaccines include Pandemic 2009 H1N1 strain. Live attenuated influenza vaccines are available, but not in India.

Biologically, IIV are either split-virion or sub-unit vaccines, produced from highly purified and inactivated virus grown on embryonated hen eggs.

Composition of the influenza vaccines is changed annualy due to phenomena of antigenic shift and drift (Ch 10.26). WHO recommends two different set of vaccine strains every year-one for northern hemisphere in February and another for southern hemisphere countries in September. While entire India is in northern hemisphere, southern hemisphere vaccines are considered as more appropriate here, especially for south India.

Supply and storage: IIVs contain 7.5 or 15 µg hemagglutinin of each component strain, supplied as 0.25 or 0.5 ml single-dose vials or prefilled syringes, to be stored at 2–8°C.

Dosage and administration: IAP recommends a *uniform dose of 0.5 ml for all children* above 6 months of age, though some manufacturers recommend a lower dose of 0.25 ml in children <3 years due to higher reactogenicity and risk of febrile seizures in younger age group.

Immunization schedule: Not included in NIS, IAP recommends Influenza vaccination to all children from 6 months to 5 years of age, and in high-risk children beyond this age. Two doses at 4 weeks interval are recommended in first year of vaccination in children <9 years, followed by a single dose annually preferably just before the onset of peak influenza season. In children aged 9 years or above, adolescents or adults, only single dose is recommended, even if not vaccinated earlier

Protective efficacy: Reported efficacy of IIVs is ~59% for confirmed influenza and 36% for all influenza-like-illnesses, for one year.

Side-effects: IIVs are generally safe except for local reactions, higher risk of febrile seizures and rare risk of Guillain-Barré syndrome in some cases.

Contraindications: IIVs should be avoided in cases with egg allergy or past history of Guillain-Barré syndrome, unless expected benefits outweigh risks.

9.2.3 VACCINES FOR SELECTIVE USE

These vaccines are not recommended for routine immunization of Indian children, but only in high-risk children. While discussed in detail in relevant chapters on infections, some important selective-use vaccines include:

- **Anti-rabies vaccine (ARV)** for post-exposure prophylaxis after dog-bite or pre-exposure prophylaxis to occupational animal handlers (Ch 10.27).
- **Meningococcal vaccines** for: (a) international travellers, e.g. students going abroad for studies or (b) high-risk children with complement deficiency, anatomical or functional asplenia, splenectomy or sickle cell disease, (c) health care workers likely to be exposed to infection and for post-exposure prophylaxis in some cases (Ch 10.10).
- **Cholera vaccine for** residents and travellers of highly endemic regions and high-risk circumstances for the outbreaks, e.g. Kumbh mela. (Ch 10.11).
- **Yellow fever vaccine** for travellers to some African/South American countries. It is a live attenuated vaccine, given as single dose 0.5 ml SC, which fulfills the travel requirements (International certificate of vaccination and prophylaxis) valid for life. Efficacy is ~100% for at least 10 years. While generally safe, yellow fever vaccine carries a rare risk of Yellow fever vaccine associated neurological disease (YELAND) or viscerotropic disease (YELAVD).

9.2.4 NEWER VACCINES

Newer vaccines is a loosely-defined term encompassing large number of vaccines which are: (a) already available but not yet licensed in the country or (b) still in trial phase under development.

These vaccines include either the alternatives to the existing vaccines or vaccines against the diseases for which no vaccine is available till now. While detailed discussion on these vaccines beyond the scope of this book two newer vaccines deserve mention.

Dengue vaccine: CYD-TDV (Dengvaxia®) is the first and only licensed vaccine against dengue, being used in some endemic countries of Asia and Latin America, though several other candidates are under development.

Contents: CYD-TDV is a live attenuated, recombinant tetravalent vaccine containing four recombinant dengue serotypes.

Supply and storage: It is a freeze-dried single-dose or multi-dose formulation, to be reconstituted using 0.4% sodium chloride diluent (0.9% for multi-dose vials), before use. It should be stored at 2–8°C and used within 6 hours of reconstitution.

Immunization schedule includes total three doses of 0.5 ml subcutaneously, given at 6 months interval. While vaccine is licensed for use between 9–45 years of age, the optimal age of vaccination depends on local disease epidemiology (see WHO recommendations below).

Efficacy: Immunogenicity of the vaccine is higher in vaccinees who are seropositive to any serotype, (i.e. had evidence of prior dengue infection) before vaccination than in baseline sero-negative vaccinees.

Protective efficacy in trial participants aged 2–16 years was reported to be ~43%–76.9% for different serotypes, higher against the hospitalization and severe disease than in preventing symptomatic disease of any severity.

Safety: Side-effects include transient local reactions and minor systemic reactions, e.g. myalgia, headache and malaise in about half of the cases.

Outcome of CYD-TDV vaccination differs in sero-positive and seronegative individuals at the time of vaccination. In seropositive individuals, the vaccine acts as second infection with an attenuated virus, thus offering the protection but without complications. In seronegative individuals, the vaccine acts as the first infection, eliciting immune response. If these vaccinated case acquires second infection by wild virus, disease tends to be more severe as in the case of second of two natural infections in unvaccinated individuals.

WHO Global Advisory Committee on Vaccine Safety (GACVS) recommends that individuals who have not been infected with wild dengue virus (seronegative), should not be vaccinated with CYD-TDV as it confers a low level of protection during first 2 years but later followed by an increased risk of hospitalized and severe dengue.

Contraindications include severe immunodeficiency or allergic reaction to previous doses, apart from pregnancy and lactation.

WHO Recommends that

- Countries should consider introduction of the dengue vaccine CYD-TDV *only* if the minimization of risk among seronegative individuals can be assured.
- For countries considering vaccination in dengue control program, *pre-vaccination screening* is the recommended strategy, followed by vaccination of *only* seropositive subjects.
- If pre-vaccination screening is not feasible, vaccination without individual screening could be considered in areas with seroprevalence rates of at least 80% by the age 9 years.

Malaria vaccine: RTS, S (Mosquirix®) is the only vaccine against malaria licensed on pilot basis (2019) in three sub-Saharan African countries – Ghana, Kenya and Malawi, which has shown significant reduction in prevalence as well as severity of falciparum malaria. Recently, an indigenous malaria vaccine developed by Serum Institute of India *(R21/Matrix-MTM)* has also received WHO approval, though yet to be launched.

Contents: RTS, S is a pre-erythrocytic stage hybrid recombinant protein vaccine containing *P. falciparum* sporozoite protein fused with HBV surface antigen.

Supply and storage: RTS, S is a freeze-dried powder and needs to be reconstituted before use. It must be stored at 2–8 C and used within 6 hours of reconstitution.

Immunization schedule: As of now, the vaccine has been used only in children aged 5–17 months, given as 0.5 ml IM with four dose schedule-three doses at one month interval, followed by a fourth dose after 18 months.

Efficacy: Vaccine induces humoral as well as cellular response to prevent maturation and multiplication of sporozoites in liver. It has shown ~39% efficacy against the disease *per se* and 29% against the severe malaria on four years follow-up, along with significant reduction in hospitalizations and need for blood transfusions. Vaccine does not offer any protection against *P. vivax* malaria.

Safety: Vaccine is well tolerated except local side effects and increased risk of febrile seizures.

COVID vaccines: While many COVID-19 vaccines are available for Indian adults, very few have received approval for use in children. COVID immunization of children in India <18 years was started 16th March 2022, and as of now four COVID vaccines have used *emergency use authorization* (EUA) from Drug Controller General of India (DCGI) for children, as follows:

- **Covaxin** (Bharat Biotech) is being given to children >15 years as two dose schedule at 4–6 weeks interval by the government, though it has also received EUA for children above 6 years of age. Vaccine is also available for private sector.

- **Corbevax** (Biological E Limited) is being given to children >12 years (even for 12–14 years age group) as two dose schedule at 28 days interval by the government, though it has also received EUA for children above 5 years of age. Vaccine is also available for private sector.
- **Covovax** (Serum Institute of India) can be used in children >12 years with two doses at 21 days interval, though it has also received EUA for children above 7 years of age. However, it is not available through government centers.
- **ZyCoV-D** (Zydus cadila), first needle-less and first DNA Plasmid vaccine has also received EUA for children >12 years, though not provided though government centers.

9.2.5 COMBINATION VACCINES

Combination vaccines are immunization products which contain antigens of multiple infectious agents, e.g. DPT or MMR. However, vaccines which contain multiple strains of the same infectious agent, e.g. PCV, are better described as ***polyvalent vaccines***.

Combination vaccines containing two to six antigens are available in India at present **(Table 9.3)** and many more combination vaccines are being introduced in market.

Main advantage of combination vaccines is less number of pricks and fewer immunization visits with better compliance. However, these vaccines carry potential disadvantage of cumulative risk of adverse events. Human immune system is capable to respond to large number of antigens simultaneously and efficacy of most vaccines is not altered by concurrent administration as combination vaccines.

IAP recommends use of combination vaccines with following caveats:

- All licensed combination vaccines have an immunogenicity, efficacy and safety profile similar to separately administered component vaccines;
- Multiple vaccines should not be mixed in the same syringe, to prepare indigenous combination vaccine, unless specifically recommended by manufacturers.

TABLE 9.3: Combination vaccines available in India

Number of antigens	*Combination*
Bivalent (Two antigen) vaccines	DT or Td*
	MR*
	HAV+HBV
Trivalent (Three antigen) vaccines	DTwP, DTaP
	MMR
Quadrivalent (Four antigen) vaccines	DTwP+Hib
	DTwP+HBV
	DTaP+IPV
	MMRV
Pentavalent (Five antigen) vaccines	DTwP+HBV+Hib*
	DTaP+HBV+Hib
Hexavalent (Six antigen) vaccines	DTwP+HBV+Hib+IPV
	DTaP+HBV+Hib+IPV

*Combination vaccines used in NIS

9.3 IMMUNIZATION SCHEDULES

Immunization schedules vary from country to country and need to be revised time to time, depending on the: (a) local disease prevalence, (b) epidemiological features, e.g. common age of infection, (c) availability of safe and effective vaccine, (d) economic feasibility and cost-effectiveness, and (e) logistic considerations.

An appropriate immunization schedule should cover (a) as many prevalent diseases as possible, (b) as early as possible before the exposure to infection and (c) with minimum number of clinic visits to avoid inconvenience to parents and *drop-outs*.

Currently, two immunization schedules are followed in India – *National Immunization Schedule (NIS)* for immunization of general population through public resources and *IAP Immunization Schedule* recommended by Indian Academy of Pediatrics, for use in an individual child through private sector. Both schedules are often complementary and not contradictory.

9.3.1 NATIONAL IMMUNIZATION SCHEDULE

National Immunization Schedule (NIS) in India presently aims to prevent eleven diseases, i.e. Tuberculosis, Diphtheria, Pertussis, Tetanus, Poliomyelitis, Hepatitis B, H. influenzae B, Rotavirus, Pneumococcal infections, Measles and Rubella using nine vaccines, i.e. BCG, HBV, OPV, Pentavalent V, IPV, RV, PCV, MR and Td vaccines, apart from Japanese encephalitis vaccines in selected endemic districts **(Table 9.4)**.

This schedule has been adopted in all national child health programs and vaccines are provided by the government, free of charge.

TABLE 9.4: National immunization schedule

Age	*Vaccine*
Birth*	BCG* + OPV_0+ HBV_0
6 weeks	$DTwP_1$ + HBV_1 + Hib_1 + OPV_1 + $_fIPV_1$ + RV_1 + PCV_1
10 weeks	$DTwP_2$ + HBV_2 + Hib_2 + OPV_2 + RV_2
14 weeks	$DTwP_3$ + HBV_3 + Hib_3 + OPV_3 + $_fIPV_2$ + RV_3 + PCV_2
9–12 months	MR_1 + JE_1** + $_fIPV_3$ + PCV_3 (with Vit A_1***)
16–24 months	DTwP (B_1) + OPV (B) + MR_2 + JE_2**
5–6 years	DTwP (B_2)
10 years	Td
16 years	Td
Pregnancy	Td-Two doses in early pregnancy at 0,4 weeks Single dose only, if 2 doses received in last 3 years

* At birth in institutional deliveries/or at 6 weeks. **$_f$IPV:** Fractionated IPV

** JE vaccine only in endemic districts.

*** Vitamin A to be repeated every 6 months till 3 years

9.3.2 INDIAN ACADEMY OF PEDIATRICS (IAP) SCHEDULE

Indian Academy of Pediatrics (IAP) schedule NIS is the most practical but not necessarily an ideal schedule, as many useful vaccines have been left-out due to cost considerations or given at less than most appropriate age due to logistic considerations of a public health program.

IAP recommends more comprehensive immunization schedule, **(Fig. 9.2)** revised time to time in view of current disease patterns. Important differences between these two schedules are as follows. IAP recommends:

- *Seven additional vaccines* for universal immunization other than those included in NIS, i.e. TCV, IIV, HAV, MMR, varicella, Tdap and HPV. However, HPV is likely to be included in NIS soon.
- *Only one dose of OPV* at birth instead of total five doses at different ages in NIS.
- *Five intramuscular IPV doses*, including three primary doses at 6, 10, 14 weeks and two boosters at 16–18 months and 5–6 years, instead of three intradermal fractionated IPV doses at 6 and 10 weeks and 9 months.
- Use of DTwP or *DTaP,* instead of DTwP used in NIS.
- Single dose of *Tdap* (a) to all fully immunized children at 11–12 years instead of Td booster in NIS, (b) in partially immunized children at 7 years, who had missed second DPT booster, and (c) as first dose of catch-up immunization 7 years of age. It also recommends to replace all Td doses in pregnancy with Tdap.
- *Last HBV dose* should be administered not before 24 weeks of age and at least 16 weeks after first dose, whichever is later, instead of 14 weeks of age in NIS.
- *Four doses of PCV* at 6,10,14 weeks with a booster at 15 months instead of three doses at 6 weeks, 10 weeks and 9 months in NIS.
- *First dose of RV should not be given > 15 months and no dose after 32 weeks.* NIS provides RV til 1 years of age, though subsequent doses may be given even later if first dose was given before 1 year.
- *Three doses of MMR* at 9 months, 15 months and 4–6 years instead of 2 doses of MR (no MMR) at 9–12 months and 16–24 months in NIS.
- IAP also prescribes *catch-up immunization for children above 5 years*, while NIS is largely focussed on infants and children below 5 years.

9.3.3 MISSED (CATCH-UP) IMMUNIZATION

Despite best efforts, overall immunization coverage in India for UIP vaccines is ~76% (NFHS-V 2020–21) and substantial number of children miss vaccinations on due ages. To immunize them at earliest possible opportunity, following principles must be followed for catch-up immunization:

- Catch-up schedule must be tailored to achieve age-appropriate immunization as early as possible with minimum number of visits but without compromising basic principles, e.g. minimum dose interval, etc.

Fig. 9.2: IAP immunization schedule.

a: Within 24 h after birth; **b:** Extra dose permitted in combination vaccine; **c:** Can be given as combination vaccine; **d:** Not required for RV1; **e:** Preferably pre-monsoon, then single dose annually till 5 years age; **f:** Single dose for live vaccine; **g:** Second dose after 3–6 mo; **h:** After 7 years of age if second DPT booster not received, else single dose at 10–12 years, use Td, if Tdap not available; **i:** Two doses <14 years, 6 mo apart; **j:** Three doses after 14 years or in immunocompromised persons, **k:** Menactra® is approved as 2-doses between 9–23 mo at 3 months interval, Menveo® as single dose only after 2 years age

TABLE 9.5 : Catch-up (Missed) immunization

Vaccine (age limit)	*Schedule*
BCG (5 yr)	Single dose
DPT (None)	Age < 7 yr: DTwP at 0,1,6 mo, B after 6 mo[1] Age >7 yr: Tdap > Td > Td at 0,1,6 mo
IPV (5 yr)	3 doses at 0,1,6 mo or 2 doses at 0,2 mo or Single dose if received only bOPV (born after 25.4.2016)
HBV (None)	Three doses at 0,1,6 mo
Hib (5 yr)	*Age 6–12 mo:* 2 doses at 0, 1 mo, B after 8 weeks Age 12–15 mo: Single dose, B after 8 weeks Age 15 mo-5 yr : Single dose, no booster
RV (32 wks)	Two/Three doses at monthly interval[2]
PCV (5 yr)	Age 6–12 mo: 2-doses at 0,1 mo-B in 2nd year Age >12–23 mo: 2-doses at 0,1 mo, no booster Age > 23 mo: 2-dose PCV 10 (0,2 mo)/1-dose PCV 13
MMR (None)	Two doses at 0,1 mo
JE (18 yr)	Two doses at 0,3 mo
HAV[4] (10 yr)	Two doses at 0,6 mo (Inactivated) or Single dose (Live HAV)
Varicella (18 yr)	< 13 yr: Two doses, 0,3 mo > 13 yr: Two doses, 0–1 mo
Typhoid (18 yr)	TCV single dose (or,TPSV every 3 years)

[1]If last dose was given before 4 years.
[2]RV *immunization* should not be initiated beyond 15 weeks of age and all doses must be completed by 32 weeks.
[3]Exclude pregnancy before vaccination in adolescent girls, due to potentially risk of CRS.
[4]Pre-vaccination screening recommended at 10 years.

Multiple vaccines may be clubbed together in same visit to reduce the catch-up time.

- Upper age limit for catch-up immunization varies with the individual vaccines, determined by the need and safety issues and must be strictly followed.
- Partially immunized children should re-start catch-up immunization from the dose which was missed earlier *and not afresh*, irrespective of the period lapsed.

NIS permits catch-up immunization till the specified age-limits for individual vaccines, i.e. till one year for BCG, PentaV, RV, PCV; five years for OPV, MR; 7 years of DPT booster and 15–16 years for Td and JE vaccine, using same number/s and interval of doses as for routine immunization. These age limits and dosage schedules have been decided for programmatic reasons to cover most vulnerable population with available resources and use a simplified uniform schedule which can be delivered through public resources.

IAP recommendations for catch-up immunization are based largely on scientific basis and hence, might differ from NIS. Upper age limits are usually higher in IAP schedule except for RV vaccines and dosage schedules may differ from those used for routine immunization **(Table 9.5)**.

TABLE 9.6: Adolescent immunization

A. Age-specific adolescent immunization	
HPV (in Girls)	Age-9–14 years: 2 doses at 0 and 6 months Age > 14 years: 3 doses at 0, 1/2. 6 months
Tdap	Single dose, then Td every 10 years[1]
B. Catch-up childhood immunization (to complete total...)	
MMR	Two doses at 4–8 weeks interval
HBV	Three doses at 0,1 and 6 months
HAV	Two doses at 0 and 6 months
TCV	Single dose
Varicella	Two doses at 4–8 weeks interval
J. encephalitis	Two doses at 0–3 months (in endemic districts)

[1]Adolescents, who have not been immunized with DPT previously, must receive two further doses of Td at one month and six month interval (0,1,6 month) to complete catch-up vaccination, which is recommended till the age of 18 years.

9.3.4 ADOLESCENT IMMUNIZATION

Many children remain unimmunized/partly immunized till they reach adolescence. Adolescent immunization offers another opportunity to fulfill these immunization gaps. It also aims to: (a) protect against diseases with higher morbidity during adolescence, e.g. Hepatitis A, varicella, (b) boost the waning immunity of early childhood vaccines, (c) counter upward shift of age-epidemiology following expanding childhood immunizations, and (d) provide vaccines more relevant in adolescent age groups, e.g. HPV or vaccines for travellers going abroad for studies.

Catch-up vaccination of adolescent girls also offers some protection to their prospective off-springs from diseases like pertussis and congenital rubella.

Table 9.6 provides a guiding schedule for adolescent immunization, though needs to be individualized.

9.4 IMMUNIZATION IN SPECIFIC SITUATIONS

In following situations, immunization schedule has to be modified according to the needs and risk of complications.

Immunocompromised children are in greater need for vaccines due to susceptibility for infections but benefits may not be optimal due to poor immunological response. Further, there is potential risk of developing active disease following administration of live vaccines. General rules of immunization in these children include that:

- Live vaccines are contraindicated in severe immunodeficiency, but may be given in mild/moderate immunodeficiency, provided benefits outweigh the risks;
- Inactivated vaccines may be given but the protective value is unreliable and must be checked periodically

with antibody titers. If necessary, doses need to be repeated. Higher quantity or number of doses may be used in such cases, e.g. double-dose HBV.

- Household contacts of immunocompromised child should also be fully immunized to reduce the risk of exposure. However, they should not be given transmissible vaccines, e.g. OPV.

All routine vaccines, including live vaccines, may be given to asymptomatic HIV positive children without laboratory evidence of immunosuppression. However, live vaccines, e.g. BCG, OPV, measles and varicella are contraindicated in seropositive children with clinical AIDS or severely low CD4 counts. Inactivated vaccines are safe. IPV may be used instead of OPV in these cases (Ch 10.28).

Cancer chemotherapy: All live vaccines are contraindicated for 6 months after completion of therapy and inactivated vaccines may be given but should not be counted as valid doses. General considerations for immunization of a child on chemotherapy are as follows:

- No vaccine must be given during chemotherapy including pulse polio doses, except influenza (annual dose) and HBV (in unimmunized/partly immunized children).
- Influenza and varicella vaccines are also recommended for the contacts, who should not receive OPV including Pulse polio dose (replace with IPV, if needed). If given by mistake, contact sibling should remain away from cancer child for 2 weeks.
- Post-exposure prophylaxis for rabies must include passive prophylaxis for all bite categories and one additional dose of ARV at 90 days.
- Tetanus prophylaxis in wound care must include single Td dose irrespective of past immunization status, and tetanus immunoglobulins in all cases except in clean and minor wounds.
- Post-exposure varicella prophylaxis is must with VZIG, IVIG or high dose acyclovir in exposed children.
- Post-chemotherapy, immunization depends on the previous immunization status and should begin only after 6 months of completion of chemotherapy. While unimmunized or partially immunized children should receive catch-up immunization as usual, fully immunized children before chemotherapy should receive *a single booster dose* of age appropriate DPT, IPV, HBV, Hib, PCV, HAV, TCV, MMR and varicella. In children, who had received only OPV doses in the past, two IPV doses at one month interval are recommended.

Long-term steroid therapy: Efficacy of inactivated vaccines as well as safety and efficacy of live vaccines is doubtful in cases on prolonged corticosteroid therapy and general considerations for immunization in them are as follows:

- Children on low-dose systemic steroids or topical/inhaled steroids may be safely and effectively immunized with all vaccines, as also those on any dose of steroids for < 2 weeks.
- Children on high-dose oral steroids (prednisolone > 2 mg/kg/day or 20 mg/day or equivalent) for more than 2 weeks should not receive live virus vaccines until steroids have been discontinued for one month.
- Children with other immunosuppressant medications, e.g. Rituximab or TNF-α, should not receive live virus vaccines during therapy, except in special circumstances.

Preterms and LBW: Three major concerns regarding immunizations of preterm and LBW infants include high-risk of infections, uncertain immunogenicity due to immature immune system and logistic problems to give a vaccine to very small child. Some basic considerations regarding immunization of these children are as follows:

- BCG and OPV must be administered at birth irrespective of the weight or gestation, after stabilization and before discharge. However, HBV birth dose should be delayed till one month of age in babies <2000 gm at birth due to doubtful immunogenicity, *unless* delivered to an HBsAg positive mother.
- All subsequent vaccines may be given as per chronologic age (even if still in hospital), except RV vaccine, which should be deferred until discharge to prevent the health care-associated spread of virus in nursery.
- Since preterm and low birth weight babies have low muscle mass, smaller and thinner needles must be used in them for intramuscular injections.
- All HCW dealing with these babies should be appropriately immunized.

Sick children: General considerations for immunization in sick children with acute or chronic diseases, are as follows:

- Vaccinations can be safely given during *minor illnesses*, e.g. URTI, mild diarrhea, etc.
- Vaccination may be postponed during *moderate or severe acute illness* to avoid conincidental problems, e.g. febrile seizures wrongly attributed to the vaccine. However parents should be instructed to visit for immunization as soon as the child is better.
- No vaccine is contraindicated in children with *chronic systemic diseases*. In fact, special vaccines may be required in some cases, e.g. HBV in chronic liver disease, pneumococcal and influenza vaccines in cardiopulmonary disease, etc.
- Children with *hemorrhagic disorders*, e.g. haemophilia, may be given injectable vaccines subcutaneously or intramuscularly with a thinner needle and applying

the firm pressure without rubbing over the site for 5–10 minutes. In severe cases, vaccination may be given shortly after administration of clotting factor.

Blood products as well as other antibody products, e.g. immunoglobulins, (e.g. IVIG) may inhibit the immune response to live vaccines for variable period of time. Some considerations for immunization in recipients of blood or antibody products are as follows:

- All except live vaccines can be administered simultaneously, before or after an antibody-containing product without any interval criteria, but at different sites.
- MR/MMR and varicella vaccines should not be given until 6 months after blood product transfusions (3 months after saline washed RBCs), 10 months after IVIG, and 3–4 months after other specific immunoglobulins. Administration of an antibody-containing product within 14 days of MR/MMR or varicella vaccination might affect the vaccine uptake and the dose should be repeated after recommended time interval.
- Other live vaccines, e.g. yellow fever, Rotavirus vaccine, live attenuated influenza vaccine, and zoster vaccines may be given anytime.
- Low dose anti-D globulin to Rh-negative women is not an indication to defer rubella or varicella vaccination.
- HBV, TT/Td and ARV vaccines may be given simultaneously with corresponding immunogobulins but at different sites.

Solid organ transplant (SOT) recipients are immunocompromised even before the transplant due to the underlying disease and continue to be the same after procedure due to immunosuppressive therapy or graft rejection. Important considerations related to immunization for recipients are as follows:

- SOT recipients should complete all age-appropriate immunizations prior to the transplant, at least 2 weeks before the transplant (4 weeks for live vaccines), followed documentation of antibody titers. If required, varicella and MMR vaccines may be given even at 6–11 months of age.
- Post-transplant, live vaccines are contraindicated though catch-up immunization with other vaccines may be started after 6 months. IIV can be given after 1–2 months of transplant and then annually. Antibody titers may be checked after 6 months to decide the need for boosters, e.g. HBV booster.
- Household and health-care contacts of SOT recipients should be immunized with live vaccines, e.g. MMR, varicella etc and influenza to reduce the risk of transmission.

Haematopoietic stem cell transplant (HSCT) recipients are virtually unimmunized due to loss of all memory responses during marrow ablation and need to be re-immunized. Basic considerations in immunization of these cases are as follows:

- Age-appropriate immunization of the donor and recipients should be completed, at least 4 weeks before for live vaccines and 2 weeks before inactivated vaccines.
- Post-HSCT, recipients should be considered as *"never vaccinated"* regardless of pre-HSCT vaccination status and need to be *re-immunized* with all inactivated vaccines, after 6 months of procedure. However, IPV, Hib, PCV and IIV can be given after 3–4 months. Additional doses may be needed for HBV or PCV13.
- Live vaccines should not be administered to HSCT patients with active GVHD or ongoing immunosuppression. MMR and varicella vaccines may be administered after 24 months, if the recipient is presumed to be immunocompetent and 8–11 months after last dose of IVIG.

Splenic dysfunction due to congenital asplenia or secondary to sickle cell disease, splenectomy or radiation therapy render children susceptible for serious infections with encapsulated organisms and important immunization considerations in these cases are as follows:

- No vaccine, including live vaccines, is contraindicated and they should all receive all age-appropriate immunizations, with special emphasis on PCV, Hib, and typhoid vaccines.
- In addition, they should also receive: (a) two doses of MCV at 8 weeks interval after 2 years of age, (b) single dose of Hib vaccine, if not received till 5 years of age, (c) age-appropriate dose/s of PCV, and (d) asingle dose of PPSV after 8 weeks of PCV (and at least 2 weeks before surgery). PPSV must be repeated once after 5 years.
- For *emergency splenectomy*, vaccination should begin at least 2 weeks after the surgery rather than immediately, for better antibody response with: (a) MCV_1, PCV and Hib (if not received earlier), followed after 8 week by (b) MCV_2 and PPSV. PPSV must be repeated once after 5 years.

9.5 IMMUNIZATION PROGRAMS

Operative strategies to achieve adequate immunization keep on changing according to the needs and evaluation assessments. This chapter deals with some important strategies and program to deliver immunization services.

9.5.1 UNIVERSAL IMMUNIZATION PROGRAM

Universal immunization program (UIP), launched on November 19th 1985 to enhance immunization coverage in India, is currently a component of *Reproductive*

Maternal, Newborn, Child and Adolescent Approach (RMNCH+A) since 2013, under National Health Mission.

India has one of the largest immunization program in the world targeting 2.6 crore newborns each year. First country-wide immunization program in India, i.e. *expanded program of immunization* (EPI) was launched in 1978, which was later modified as *universal immunization program* (UIP) to widen the coverage. In 1992, it was incorporated in *Child Survival and Safe Motherhood Program* and then in *Reproductive and Child Health Program* (1997) under *National Rural Health Mission* (2005) and then *National Health Mission* (2013).

Aims: UIP currently aims to provide coverage against twelve vaccine preventable diseases in infants (*tuberculosis, poliomyelitis, diphtheria, pertussis, tetanus, hepatitis B, H. influenzae B, rotavirus, pneumococci, measles* and *rubella)* as well as *Japanese encephalitis* in endemic districts, using National Immunization Schedule (NIS). It also provides for tetanus immunization in pregnant mothers.

Components: Important components of UIP are:

- Universal immunization of infants and pregnant mothers,
- Improved vaccine production and quality control,
- Spread of public awareness,
- Training of health personnel, and
- Surveillance of vaccine preventable diseases.

Strategies: Important strategies adopted by UIP are as follows:

- *For universal immunization:*
  - Routine immunization as per NIS,
  - Intensified immunization programs, e.g. Mission Indradhanush, pulse polio immunization, MR campaign
  - Targeted immunization in high-risk areas, e.g. mop-up rounds.
- *For vaccine production:*
  - Encourage and support private sector participation.
  - Increasing production in public sector.

  India is self-sufficient in production of all UIP vaccines except OPV.
- *For quality control:*
  - Maintenance of adequate cold-chain.
  - Batch-wise testing of vaccines at production/import level and random testing at field level.
  - Adequate supply of refrigerators, vaccination materials, e.g. syringes, etc. and *electricity*.
- *For public awareness:*
  - Information, education and counseling (IEC) activities, using mass-media.
  - Involvement of local community leaders and non-governmental organizations.
- *For regular training:*
  - Periodic training of field workers.
  - Distribution of training material and guidelines.
- *For vaccine surveillance:*
  - Periodic immunization coverage studies.
  - Periodic review of the local disease prevalence.

Evaluation: Reported coverage for all UIP vaccines in India at present is ~76.4% according to NFHS-5 2021 data **(Table 28.3)**, with best coverage for BCG (95.2%) and least for second dose of MR (31.9%). There is also gross disparity between immunization coverage in different states and urban *vs.* rural areas.

While targeted 100% immunization coverage is yet to be achieved, success of this program is reflected in marked decline in morbidity and mortality rates due to vaccine preventable diseases.

9.5.2 MISSION INDRADHANUSH

Mission Indradhanush was launched on 25th December, 2014 with an objective to ensure full (>90%) immunization of children below two years by 2020 and pregnant women by year 2020, specially in low-coverage districts. *Indradhanush* represents seven colors of rainbow—targets to immunize against seven vaccine preventable diseases—*tuberculosis, diphtheria, pertussis, tetanus, polio, hepatitis B and measles,* initially included in the program.

First phase began on 7th April, 2015, the World Health Day, with four week-long monthly rounds of intensified immunization in selected high-priority districts with <50% immunization coverage. Within the districts, the mission focused on high-risk settlements of nomads and migrant labor, forest-dwellers, tribal regions, inaccessible geographical areas and urban slums. Zinc tablets and ORS packets were also freely distributed during these rounds to protect against diarrhea.

Since then, the program has been conducted in different phases, the latest being **Intensified Mission Indradhanush 5.0,** launched in 2023. Unlike previous phases, Mission Indradhanush 5.0 covered whole country (rather than high-priority populations) with three rounds at monthly interval to provide all *due/missed* vaccines under NIS to children below 2 years.

Global alliance for vaccine and immunization (GAVI): GAVI is an international coalition of funding agencies, National Health Programs of various countries and NGOs to independently fund or raise new resources: (a) to improvement of immunization services and coverage in developing countries, (b) to fund research and development activities for newer vaccines, and (c) to promote safe immunization practices. India mainly receives GAVI support for HBV and pentavalent vaccine along with supply of vaccination equipment and injection safety programs.

9.6 COLD CHAIN SYSTEM

Vaccines, being the biological agents, are likely to lose their potency when exposed to higher (or lower) than the recommended environmental temperature. This exposure can occur at the level of manufacture, transport, storage or administration.

Loss of vaccine potency depends not only on the degree of temperature but also on the duration of exposure and type of vaccine. Live vaccines, e.g. OPV and measles are most heat-sensitive and lose their potency rapidly on heat exposure. Inactivated vaccines, specially those containing aluminium adjuvants, e.g. DTwP/DTaP/HBV, HAV, HPV and PCV are usually more heat stable but should never be frozen, as they deteriorate on thawing.

Cold chain is an operational term to define *a system of transporting and storing the vaccines at recommended temperatures from the manufacturers' level till the point of administration*. *Desired temperature zones* for storage and transport of most vaccines is:

For short-term (1–2 months) storage: 2–8°C

For long-term storage: –20°C

In addition, lyophilized vaccines, e.g. BCG, MR/MMR, varicella and rotavirus vaccines are also sensitive to light exposure.

Components: Essential components of cold chain include:

- Supply of *appropriate pieces of equipment* to maintain the desired temperature during transport, storage and immunization sessions,
- Provision of *quick transport* facilities to decrease the risk of exposure to high temperatures,
- *Training of the people*, who organize and manage vaccine distribution,
- Continuous as well as periodic *surveillance* for efficacy of cold-chain maintenance.

Tools (equipment) to maintain adequate cold chain system include **(Table 9.7)**:

- *Walk-in coolers* to store large amounts of vaccines at the state and/or regional centers.
- *Deep freezers* for long-term storage of OPV and MR/MMR vaccine at –20°C.
- *Ice-lined refrigerators (ILR)* are top-open refrigerators, acting as a buffer in case of power failure.
- *Purpose-built or dedicated refrigerator* is essential equipment for the routine storage of vaccines at clinics and small hospitals. In refrigerators, *OPV vaccine should be kept in freezer compartment, BCG, MR/MMR and varicella vaccines on the top-shelf, other vaccines in middle-shelf/s, and diluents in the lower-most shelf* **(Fig. 9.3)**. A dial thermometer should be kept in the upper-shelf to monitor the temperature.

TABLE 9.7: Common cold-chain equipment used under UIP at different storage centers

Site	*For OPV*	*For other vaccines*
Central and state Depots	Walk-in-freezer (–15 to-25°C)	Walk-in-cooler (2–8°C)
District centers	Deep freezer (–15 to-25°C)	ILR (2–8°C)
Primary health center	ILR (2–8°C)	ILR (2–8°C)
Sub-centers	Cold boxes (2–8°C)	Cold boxes (2–8°C)
Immunization sites	Vaccine carrier (2–8°C)	Vaccine carrier (2–8°C)
Private practice	Purpose built Refrigerator* (2–8°C)	Purpose built Refrigerator (2–8°C)

Hold-over time (at 43°C): Deep freezer 2.5 hours, ILR 20 hours, cold box 48–96 hour, vaccine carrier 36 hours

* Avoid domestic refrigerators

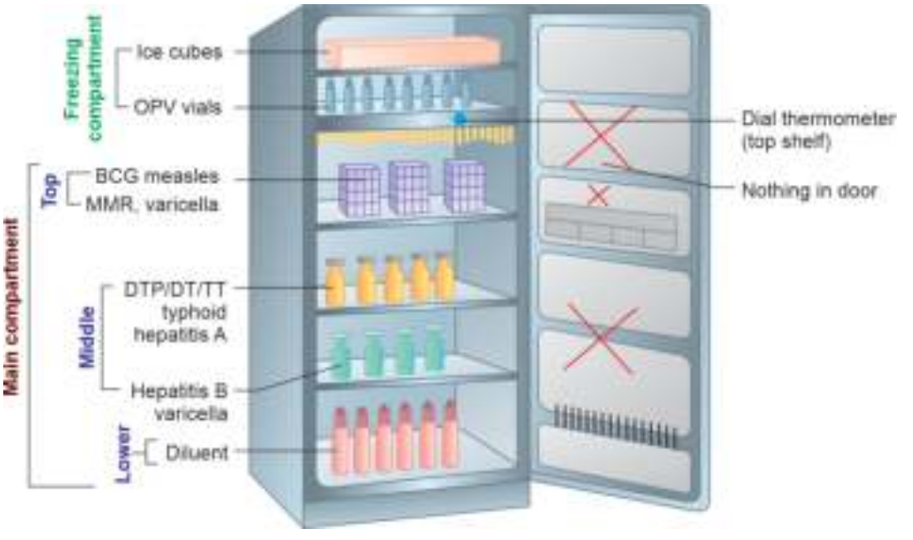

Fig. 9.3: Correct method of vaccine storage in refrigerator.

Fig. 9.4: Vaccine carrier.

Enough ice cubes and vaccine carrier packs should be kept in the freezer compartment to keep the vaccines cool in case of power failure. Nothing should be kept in the door of the refrigerator.

Refrigerators used for vaccine storage, should not be used for any other purpose, e.g. water/drug storage, to avoid unnecessary opening of doors.

Domestic refrigerators should not be used for storage of vaccines due to wild temperature fluctuations during frosting-defrosting cycles and frequent door opening. However if used in absence of alternatives, it should be: (a) frost-free with no heating cycles, (b) have separate door for freezer, (c) accessible only to vaccination staff and not used to store other things, e.g. water, and (d) temperature is maintained at 2–8°C with freezer temperature below –5°F (–15°C).

- *Vaccine carriers or isothermic boxes* are used to carry small amounts of vaccines from refrigerator to the site of immunization session. In these carriers, safe temperature can be maintained for 6–8 hours. Frozen ice packs are used to line the side of the box and a dial thermometer should be kept inside to record the temperature. The vials of DTwP/Td should first be wrapped in plastic sheets before keeping inside, to avoid freezing **(Fig. 9.4)**.

Vaccine van is an insulated van used for bulk transport of vaccines from central or regional depots to district centers. Vaccines should be transported only in cold boxes, which should be loaded in the vaccine van immediately after packing. At destination, these boxes must be unloaded as early as possible and vaccines should be transferred to the ILR immediately.

Monitoring of cold chain is done by: (a) regular check with dial thermometers, (b) vaccine-vial monitors, and (c) random collection of vaccine samples from distribution and field sites for laboratory potency testing. Some other monitoring tools include freeze-indicators, data-loggers and other types of thermometers.

Fig. 9.5: Vaccine vial monitor.

Vaccine Vial Monitor (VVM) is a sticker fixed over many of the heat-sensitive vaccine vials to identify whether the vaccine has been damaged by exposure to heat and should not be used. It includes a lighter square made of a heat-sensitive material inside a darker circle. On exposure to higher ambient temperatures, the color of the square darkens irreversibly. *If the color of square is darker or matching the outer circle, vaccine is probably not potent and should be discarded* **(Fig. 9.5)**.

VVMs are unique to each vaccine and are of four types: VVM 30, VVM 14, VVM 7 and VVM 2, with the number corresponding to the number of days the vaccine remains potent on exposure at +37°C. In combination vaccines, the VVM corresponds to the most heat-sensitive component of the vaccines, e.g. VVM on DPT vial corresponds to the pertussis component of the vaccine.

VVM is not a substitute of expiry date and vaccine may also degrade due to other factors, e.g. light exposure, which is not indicated by VVM.

9.7 ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

All vaccines are extremely, but not absolutely, safe and adverse reactions are rare but do occur after vaccinations.

Definition: *Adverse event following immunization* (AEFI) is defined as "*an untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine*." This adverse event may be any unfavorable or unintended sign, an abnormal laboratory finding, a symptom or a disease.

Classification: AEFI are classified according to the probable cause, frequency and severity.

Causality-wise, AEFIs are classified according to probable cause, as follows:

- ***Vaccine-product related reaction,*** due to inherent property of the vaccine product/s, e.g. VAPP following OPV or febrile seizure following DTwP vaccination.
- ***Vaccine-quality defect related reaction,*** due to rare qualitative defect/s in the vaccine or its delivery device provided by manufacturer, e.g. insufficient inactivation of the constituent pathogen or contamination during manufacturing process.
- ***Immunization-errors related reaction*** (programmatic errors), due to inappropriate handling, prescribing or administration, e.g. injection abscess, sciatic nerve injury or toxic-shock syndrome due to contamination of vials.
- ***Immunization-anxiety related reactions,*** during or before the vaccination, e.g. syncope or breath-holding spell.
- ***Coincidental events,*** due to something other than the above factors with a chance temporal association. Considering the sheer number of children immunized, these events are inevitable which can be falsely attributed to immunization.

Frequency-wise AEFI are classified as: *Very common* (>10%), *common* (1–10%), *uncommon* (0.1–1.0%), *rare* (0.01–0.1%) and *very rare* (<0.01%).

Severity-wise these reactions are classified as:

- ***Minor vaccine reactions,*** which are very common and include local reactions, e.g. pain swelling, redness, etc. at the injection site or systemic reactions, e.g. fever, irritability, malaise or others, e.g. rash after measles vaccine. These reactions may be due to the vaccine-product or other excipients.
- ***Severe AEFI*** are of minor medical significance but perceived to be severe in terms of intensity, e.g. high fever.
- ***Serious AEFI*** are potentially life-threatening, which may result in death, significant disability (including birth defects), hospitalization or require intervention to prevent permanent damage, e.g. anaphylaxis, seizures, intussusception, etc. AEFI, seen in clusters should also be considered as serious, due to adverse publicity and consequences on acceptance of immunization program.

Clinically, AEFRs may present immediately or after many days, with:

- ***Local reactions, e.g.*** pain, erythema and induration. These reactions are more common with DTwP and vaccines containing aluminum adjuvants. *Frequency of local reactions tends to increase with subsequent doses.* These reactions may be partly ameliorated by local ice packs application and paracetamol.
- ***Systemic reactions:*** Fever is the most common systemic reaction, more common with DTwP and vaccines containing aluminum-adjuvants. *These reactions tend to decline with increasing number of doses.* Although prophylactic paracetamol may reduce the incidence of post-vaccine febrile reactions, it has been found to blunt immune responses of some vaccines and should be used judiciously. Postvaccine fever rarely last for >48 hours and any fever persisting beyond this time should be evaluated for other causes.
- ***Allergic reactions*** are rare and may present with variable severity, ranging from mild urticaria to life-threatening anaphylaxis. These reactions are rarely due to the vaccine antigen, usually caused by other vaccine constituents, e.g. residual animal protein (egg), stabilizers or preservatives (thiomersol). Since occurrence of anaphylaxis cannot be predicted in most cases vaccines, all vaccines should be observed for 15 minutes and patients with history of serious allergy to any of the vaccine constituents should not receive the vaccine.

Reporting: Any health care provider, whether in public or private sector, who comes across any AEFI, must report it to local health authorities, immediately in case of:

- Serious AEFI leading to death, disability, hospitalization or occur in clusters.
- Signal and events associated with a newly introduced vaccine;
- AEFI, probably due to immunization-error related reactions;
- Any other significant events of unexplained cause within 30 days of immunization.

Causality assessment: All reported AEFIs are investigated by specialists to: (a) ascertain diagnosis and availability of sufficient data for causality assessment, (b) objectively evaluate available facts of the case on the basis of a check-list, (c) assess the strength of association on the basis of an algorithm, and (d) classify the case, as follows:

- ***Consistent*** *causal association* to immunization, with further sub-classification as the reaction being: (A1) vaccine-product related, (A2) vaccine-quality related, (A3) immunization error and (A4) anxiety-related;
- ***Indeterminate,*** with further sub-classification as (B1) consistent temporal relationship but insufficient evidence, and (B2) conflicting qualifying factors;
- ***Inconsistent*** *causal association* to immunization or coincidental, and
- ***Unclassifiable***.

9.8 SAFE IMMUNIZATION PRACTICES

Immunization is a unique medical intervention in the sense that the child is otherwise healthy and any error or compromise on the safety may have serious medical, ethical and legal dimensions apart from negative impact on the acceptability of immunization programs.

This chapter deals with important recommendations and suggestions to make immunization a safe event in practice.

9.8.1 COUNSELING AND VACCINE HESITANCY

All children should be assessed for their immunization status, preferably by reviewing their immunization card at every point of health care contact, even if they are sick or presented for different reasons. Indirect clues, e.g. presence of scar, age and site of previous vaccinations, price paid for the same in private sector, etc. may be used to identify the vaccines received earlier, if required.

A new card should be filled out, if the old immunization card is lost or not available, identifying all the vaccine/s the child needs now, including those missed earlier. Any recommended immunization schedule – NIS or IAP, may be used to customize individual vaccination requirements, with due considerations for contraindications or precautions.

Appropriate communication with parents is the key to let them appreciate the need for a vaccine and should provide information about:

- Potential risk of developing the disease or its complications.
- Efficacy of the vaccine must be informed in realistic terms. No vaccine is 100% effective and failures do occur but even then partial protection is expected to reduce the morbidity and complications.
- Safety of the vaccine must also be explained with risk of potential side effects. However, parent must be explained that benefits of vaccination outweigh the risk of side-effects and most side-effects are minor, transient and easily manageable.
- *Cost of the vaccine* is an important consideration for parents visiting private sector and should be informed in advance along with available alternatives. Parents should also be informed regarding free-of-cost availability of some vaccines under NIS.

Appropriate counseling will go a long way to alleviate parental apprehensions and ensure compliance. However, *a written consent is not necessary before vaccination* (IAP).

Vaccine hesitancy, i.e. the *reluctance or refusal to vaccinate despite the availability* of vaccines has been recognized as one of the leading threats to global health. WHO's Strategic Advisory Group of Experts (SAGE) defines vaccine hesitancy as an individual's behavior, influenced by the 3Cs ***C****onfidence,* i.e. trust or no trust in the vaccine or provider; ***C****omplacency,* i.e. perceived need or value of the vaccine, and ***C****onvenience,* i.e. ease or difficulty of access. It is the duty of HCW to identify the reason/s for vaccine hesitancy in care-givers and allay their concerns.

9.8.2 SAFE IMMUNIZATION PRACTICES

All injections involve breach in the continuity of skin hence, are potentially unsafe, according to a WHO report, ~30% of injections used for vaccinations worldwide are unsafe. A safe injection should not only harm the recipient, but also not expose the provider to avoidable risk or result in a waste that is dangerous to other people. Important recommendations of safe injection practices are as follows:

- ***Hand-washing:*** HCW should wash the hands with soap and water, if visibly dirty or may disinfect with an alcohol-based hand-rub between patients. Gloves are not necessary, though single-use gloves may be used and changed, if soiled. A HCW should avoid giving injections, if suffering from a local infection or cut which may come in contact with injected substance or blood or body fluids.
- ***Examine the vaccine product:*** Each vaccine vial must be examined for the name, expiry date and batch number, date of opening the multi-dose vial and status of vaccine vial monitor if present. Similar scrutiny is also necessary for diluents, if applicable.
- ***Prepare the vaccine:*** While many vaccines are currently available as single-dose pre-filled products, many others need to be drawn from multi-dose vials or reconstituted before use. Following precautions are necessary while preparing a vaccine for administration
  - Vaccine shot must be prepared in a clean designated area where blood or body fluid contamination is unlikely.
  - All vaccines must be prepared fresh and should not be kept as pre-filled syringes in advance.
  - Vials should be checked for cracks and leaks as well as any suspended particles in the contents before use.
  - Swabbing the vial-top with antiseptic or disinfectant is not necessary though vials may be cleaned with a dry single-use antiseptic swab and not by stored wet-cotton balls.
  - Each vaccine must be reconstituted as per manufacturer's recommendations, using *only* the diluents supplied by the manufacturer, if required.
  - Multi-dose vials carry higher risk of contamination and should be used strictly as per *Open-vial Policy.* Under *Open-vial Policy*, open multi-dose vials of some vaccines may be used in subsequent immunization sessions for up to maximum four weeks, provided: (a) expiry date has not passed, (b) vial was stored under appropriate cold-chain conditions, (c) vial septum is visibly clean and has not been submerged in water, (d) aseptic techniques were used to withdraw previous doses, and (e) vaccine vial monitor, if attached, has not reached the discard point.

- Needle used to withdraw the vaccine from this vial should not be left behind in the septum for redrawing, to avoid contamination.
- Whenever possible, vaccine shot must be prepared away from the sight of the child to avoid anxiety.

- ***Positioning the child:*** Unexpected motion at the time of injection may injure the child or cause needle-stick injuries to the HCW. Correct positioning with gentle restraining of the child is important to avoid such accidents.
  - Child is usually more comfortable in presence of mother, who should be permitted to participate in positioning of the child to minimize the anxiety.
  - Choice of the position depends on age of the child and site of administration, while *Cuddling* or *lying-down* position is preferred for infants, older children may be permitted to sit upright in mother's lap or held in the *straddle* position. School children may be immunized sitting upright independently, if cooperative **(Fig. 9.6)**.
  - Forcible restraining is not advisable, though a parent (or assistant) may tuck the child's legs between theirs to secure them or hold the child's free arm.
  - Even though the child is securely positioned and restrained, she/he should be gently informed about the injection.
- ***Route of administration:*** Vaccines are usually administered via intramuscular, subcutaneous or intradermal route **(Fig. 9.7)** as per the manufacturer's instructions or national guidelines, which are not interchangeable and should be strictly followed.
  - *Intramuscular (IM) injections* are given by piercing the skin at 90° with a longer 23–24 gauze needle. All vaccines, containing adjuvants are generally administered IM, due to higher risk of local reactions following superficial injections.
  - *Subcutaneous injections* must be administered by pinching up the skin with provider's fingers and piercing it at 45–60 angle with a shorter 23–25 gauze needle.
  - *Intradermal injections, e.g.* BCG, fIPV or ID-rabies are administered over left shoulder or upper arm using a tuberculin syringe and small 25 gauze needle, by stretching the skin between non-dominant thumb and fingers and piercing it at ~15 with the bevel of needle facing upwards. Only the needle tip should be introduced beneath the skin. A successful intradermal injection is reflected by formation of a small wheel at the site.
- ***Site of vaccination:*** NIS and other schedules generally specify the recommended site and side for each vaccine injection for the sake of uniformity, which should be adhered to unless the change is warranted due to local causes, e.g. infection, etc.
  - IM injections in infants are usually preferred over anterolateral aspect of thigh **(Fig. 9.8)** due to inadequate muscle mass in upper arm. Older children may be given IM vaccines in deltoid region. *No vaccine should be given on gluteal region as the antigen deposited in the fat may not invoke appropriate immune response*.
  - Subcutaneous injections are usually administered over outer aspect of the upper arm, though may be given over thighs in infants.
  - Intradermal injections are given over the shoulder or upper arm, conventionally on left side.
  - Two injections, when need to be given during same visit, must preferably be given on opposite sides. However, more injections can be administered on same site, separated by at least 2.5 cm to avoid overlap of local reactions.
- ***Use of sterile injection equipments:*** WHO no longer recommends the use of standard disposable syringes and needles due to risk of potential re-use. Auto-disable syringes are preferred for immunization purposes in NIS. Some important considerations while using selecting injection instrument are as follows:

Fig. 9.6: Positioning for vaccination: (A) Cuddle position; (B) Bed (lying down); (C) Upright position; (D) Straddle position.

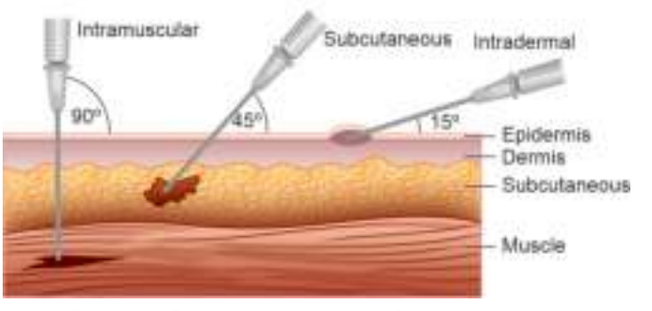

Fig. 9.7: Correct techniques of intramuscular, subcutaneous and intradermal injections.

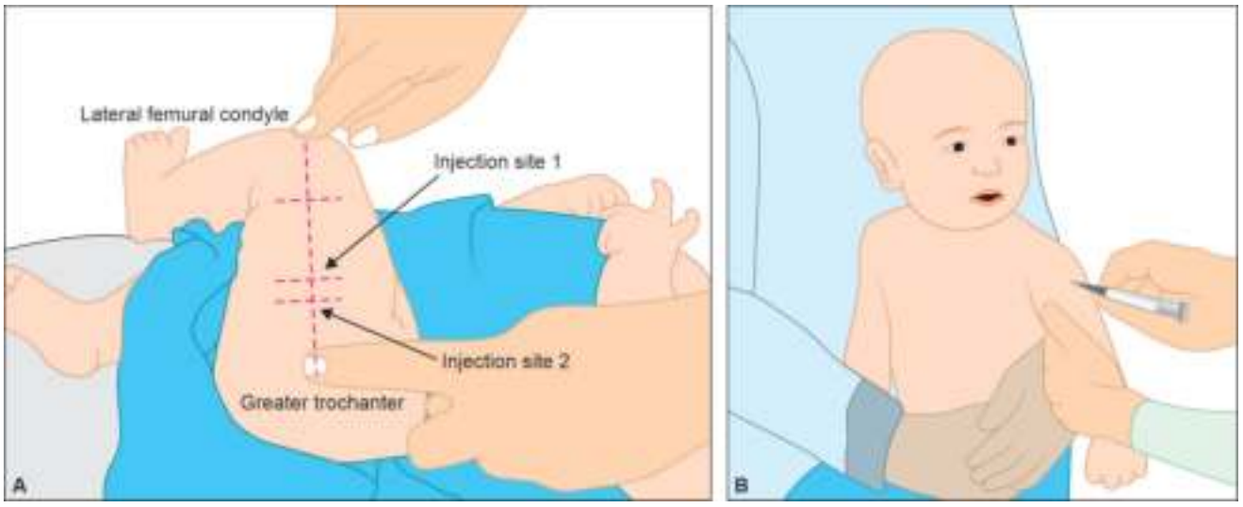

Fig. 9.8: **Correct site of immunization in infants.**
(A) Anterolateral aspect of thigh; (B) Upper arm (Deltoid region)

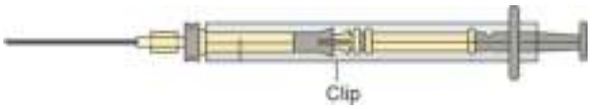

Fig. 9.9: **Autodisable syringe.**

- Package containing syringe and/or needle should be carefully inspected before opening and discarded, if found to be punctured, torn or damaged.
- Changing needles between drawing vaccine into the syringe and injecting it into the child is not necessary, unless twisted or potentially contaminated.
- A longer 23–24 Gauze needle (min 2.5 cm in length) is preferred for IM injections to reach at deeper tissue plain while shorter needles may be used for SC or ID injections.
- While using an auto-disabled syringe **(Fig. 9.9)**, plunger should not be pushed forward before the injection to inject the air in the vial, as it might disable it.

- ***Administering the injection:*** After the child is properly positioned and restrained and the injection is ready, following recommendations must be considered:
  - Selected injection site should be inspected for any local infection, etc. and must be cleaned with a swab, if dirty. Cotton swabs stored wet in a multi-use container should not be used.
  - Vigorous swabbing of the skin with antiseptic before injection is unnecessary and may add to the anxiety. Organisms colonizing the clean injection site are usually non-pathogenic. However, if an antiseptic swab is used, it should be prepared just before use and product-specific skin contact time must be adhered.
  - No antiseptic swabs should be used for local cleaning before administration of live vaccines, e.g. BCG, which may deactivate pathogens.
  - Aspiration, i.e. pulling back on the plunger after insertion of the needle but before pushing the liquid is not advised as no large vessels are present at the recommended sites and the process might be more painful for infants due to movement of needle.
- ***Waste disposal:*** Safe disposal of the injection waste is essential to prevent needle-stick injuries to HCW and re-use of contaminated injection equipments. Following recommendations must be considered for safe waste disposal:
  - Needle should be cut at the point of use only with a electric or mechanical needle-cutter and disposed-off along with part of the syringe nozzle in the puncture-proof sharps container.
  - Remaining part of plastic syringe and vaccine vial must be disposed in the red bag.
  - Empty vaccine vials/ampoules and swabs, etc. may be discarded in yellow bags.
  - *Recapping* of the used needle is a major cause of needle-stick injuries to the provider, and should be avoided. However, if necessary *single-handed scooping-re-sheathing technique* may be used to minimize the risk.
- ***Post-vaccination observation:*** All vaccinated cases must be observed for 15–30 minutes after injection for a major adverse event, e.g. anaphylaxis. All vaccination sites – fixed or outreach, must be equipped to handle anaphylaxis using anaphylaxis kits.

9.8.3 PAIN AND ANXIETY REDUCTION

Injectable vaccines are source of significant pain and anxiety which may be mitigated to some extent by some simple and effective evidence-based strategies as follows:

- HCW should be calm, reassuring and well-trained to deal with young kids. Phrases which raise the anxiety, e.g. *here comes the sting*, or promote distrust, e.g. *it will not hurt or will hurt only for a second*, must be avoided.
- Mother must be allowed to remain present during vaccination to reassure the child and hold him/her in desired position.
- Infants may be breast-fed during or shortly after the vaccination.
- Feeding small volume of sweet liquids, e.g. 1–2 ml Sugar solution before or soon after the injection might help to distract the infant and cope with the discomfort.
- Distraction measures, e.g. toys, video, music, conversation to divert attention away from pain to something more pleasant are often useful.
- Multiple vaccines, if necessary in same session, must be administered in a sequence, starting with oral ones, then less painful ID or SC injections and lastly the more painful IM injections. *WHO recommended sequence of multiple vaccines in same sitting, if required, is as follows – RV > OPV > BCG > Penta V > MR/MMR >JE.*
- Local cooling of the injection site by a topical refrigerant spray immediately before vaccination or application of a topical anesthetic 15–30 minutes before the injection has been proven to reduce the pain though cannot be used for mass immunization sessions due to logistic issues.
- Plunger should not be withdrawn after insertion of the needle to aspirate and check for blood as process may cause pain due to longer contact time and lateral movement of the needle.
- Warming the vaccine by rubbing between palms, vigorous rubbing at the injection site or prophylactic administration of an analgesic before injection is not recommended due to lack of evidence of pain-mitigation effectiveness or potential for altering vaccine effectiveness.
- Oral analgesics, e.g. paracetamol may be used to mitigate pain and/or fever after the vaccination. However, studies in children with previous febrile seizures have not demonstrated antipyretics to be effective in the prevention of febrile seizures after vaccination.

9.9 PASSIVE IMMUNIZATION

Passive immunization against specific infections or in non-specific immunodeficiency states is provided by commercial *immunoglobulins (Ig)* derived from the pooled plasma of multiple adults. These preparations contain a mixture of different *immunoglobulins* fractions, predominantly of IgG class, along with traces of IgM and IgA.

TABLE 9.8: Immunological preparations for passive immunization

Non-specific immunoglobulins
- Intravenous immunoglobulins
- Intramuscular immunoglobulins

Specific (hyperimmune) immunoglobulins
- Tetanus immunoglobulins (TIG)
- Hepatitis B immunoglobulins (HBIG)
- Varicella-zoster immunoglobulins (VZIG)
- Rabies immunoglobulins (RIG)
- Anti-D immunoglobulins

Anti-sera
- Anti-diphtheria serum (ADS)
- Anti-snake venom (ASV)

Therapeutic immunoglobulin preparations are divided into two types: (a) specific or hyperimmune immunoglobulins, and (b) non-specific immunoglobulins.

Specific (hyperimmune) immunoglobulins are prepared from pooled plasma of immunized or *convalescing* adults and contain high titers of specific antibodies against a specific antigen or infection, e.g. tetanus, diphtheria, etc. Being readymade, these antibodies ensure early protection from the specific disease by neutralization of circulating antigen or toxin. However, this protection is limited and temporary, due to quantitatively limited antibodies titers and short-life of immunoglobulins (20–35 day).

Anti-sera are purified concentrates of horse sera, who have been actively immunized with a specific antigen and provide passive immunity to a specific infection, e.g. diphtheria, tetanus and snake bite.

Currently available specific immunoglobulins **(Table 9.8)** are highly-refined biological products of human, which have gradually replaced earlier products of equine origin.

However two anti-sera of equine origin are still in common use due to lack of alternatives including anti-diphtheria serum (ADS) and anti-snake venom (ASV), which carry high-risk of adverse reactions, e.g. anaphylaxis, serum sickness, etc. Indications and dosage of these products are discussed in respective chapters.

Non-specific (normal) immunoglobulins are a polyvalent antibody-rich fraction, obtained from pooled human plasma that contains antibodies against several infections prevalent in general population. These immunoglobulins are available as intravenous (IVIG) as well as intramuscular (IMIG) preparations, though IMIG is rarely used at present due to slow and erratic absorption, proteolytic degradation at injection site and high-risk of adverse events, e.g. anaphylaxis. However, IMIG may still be used for post-exposure prevention of measles and hepatitis A in close contacts, with some benefits.

Intravenous immunoglobulins (IVIG) are the most promising immunomodulatory preparations, prepared

TABLE 9.9: Indications for IVIG

Definite indications:

- Immunodeficiency states
  - *Congenital:* X-linked hypogammaglobulinemia, SCID, WAS
  - *Acquired:* AIDS (prophylaxis for recurrent bacterial infection)
- Autoimmune disorders
  - Idiopathic thrombocytopenic purpura (ITP)
  - Guillain-Barré syndrome
  - Kawasaki disease
  - Chronic demyelinating inflammatory polyneuropathy

Probable uses:

- Neonatal sepsis, specially in preterms
- *Collagen disorders:* Dermatomyositis, SLE
- *Post-transplants:* Prevention of OIs and GVHD
- Autoimmune hemolytic anemia
- *Others:* Myasthenia gravis, Graves' disease, etc.

SCID: Severe combined immunodeficiency; **WAS:** Wiskott-Aldrich syndrome; **GVHD:** Graft versus host disease; **OIs:** Opportunistic infections

from pooled plasma of at least 1000 donors, with specific WHO standards. For example, (a) at least 90% intact IgG with subclasses in normal ratio, (b) free from IgG aggregates and infectious agents, and (c) low IgA content, etc.

Uses: IVIG is used as: (a) replacement therapy in various immunodeficiency states and/or (b) immunomodulatory agent in many clinical disorders **(Table 9.9)**. However, their role in some of these conditions is still experimental.

Mechanism of action: Main immunological properties of IVIG are mediated by:

- Direct neutralization of antigens, toxins and auto-antibodies,
- Structural changes and blockade of Fc receptors of autoantibodies in autoimmune disorders,
- Suppression of the synthesis of cytokines and auto antibodies and
- Other modulations in immunological network.

Adverse reactions with IVIG are rare (<5%) and usually mild, e.g. local flushing, chills and fever, etc., though fatal anaphylactic reactions have been reported in rare cases of selective IgA deficiency.

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CHAPTER

10

Infections

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10.1 FEVER IN CHILDREN

Fever, the commonest problem in pediatric practice, is defined as *the rise of body temperature over and above the normal range for age and diurnal variation*. The upper limit of normal temperature is higher in newborns (38°C) and declines gradually with increasing age, till adult level (37.2°C) is achieved by puberty. Body temperature also shows a *circadian or diurnal* rhythm, being highest in afternoon and lowest in early morning. In practice, *fever* is defined as a rectal temperature >38°C (>100.4°F), roughly equivalent to oral temperature of 37.5°C or axillary temperature of 37.2°C fever exceeding 40°C (>104°F) is generally termed as *hyperpyrexia*.

10.1.1 BASIC CONSIDERATIONS

Normal thermoregulation is controlled by a hypothalamic thermostat, i.e. *thermosensitive neurons in pre-optic or anterior hypothalamus,* which maintains the body temperature at optimal levels for normal metabolic activity. These neurons receive *afferent stimuli* form peripheral cutaneous thermoreceptors as well as endogenous sources, e.g. blood temperature; and respond accordingly to conserve/increase heat loss by various *efferent mechanisms*, e.g. cutaneous vasoconstriction/dilatation, sweating/shivering, increased/decreased urine output and behavioral responses, e.g. clothing patterns. Newborns and young infants have wider temperature fluctuations due to ineffective thermogenesis.

Pathogenesis: Fever denotes *resetting of body thermostat at higher temperature* due to variety of factors. For example:

- *Endogenous pyrogens*, produced in response to infections or inflammations, e.g. cytokines interleukins (IF-1β and IL-6), tumor necrosis factor-α (TNF-α), interferon (IFN-β and γ), stimulated leukocytes, etc.
- *Exogenous pyrogens*, e.g. microbes and microbial toxins, which either directly affect thermoregulation (endotoxins), or stimulate release of endogenous pyrogens by immunological reactions.
- *Central causes*, e.g. autonomic disturbances (Riley-Day syndrome), hyperthyroidism, etc.
- *Inadequate heat-loss mechanisms*, e.g. reduced sweating in atropine poisoning *or* ectodermal dysplasia.

Consequences: Fever is an adaptive response to a pyrogenic illness, which may be beneficial as well as detrimental. Elevated body temperature is known to decrease microbial multiplication and increase protective inflammatory response. On the other hand, adverse effects of fever include: (a) febrile seizures or fever-triggered epilepsy, (b) increased oxygen consumption (c) increased CO_2 production, and (d) metabolic acidosis/instability.

Clinically, Childhood fevers may be broadly divided into three categories:

a. Fevers with localizing signs,
b. Fevers without focus or localizing signs (Sec 10.1.2)
c. Prolonged pyrexia *or* pyrexia of unknown origin (Sec 10.1.3)

Fevers with localizing signs: Most acute febrile episodes in childhood are short duration, self-limiting and often associated with localizing signs, e.g. Coryza, cough, diarrhea, jaundice, dysuria, etc. Detailed history and examination is usually enough to arrive at the diagnosis and detailed investigations are unnecessary, except those relevant to the clinical diagnosis. However, sometimes localizing signs may be misleading and patient should be clinically evaluated *in toto* for underlying or associated health problems.

Fever without focus or localizing signs, generally defined as acute fever of <7 days duration, pose a diagnostic dilemma and require detailed evaluation to detect or exclude presence of serious bacterial infections (SBI) or occult bacteremia. Children with fever without focus are at higher risk of o*ccult bacteremia or SBI* if they have: (a) Age < 3 months, (b) immunocompromised state, c) presence of co-morbidities, e.g. severe malnutrition or chronic medical conditions, (c) ill or toxic appearance. Despite the initial impression of a fever without focus,

many of these cases are found to have subtle signs on re-evaluation or develop them during the course of illness, to assist in the diagnosis.

Prolonged fever or pyrexia of unknown origin (PUO) is generally defined as: (a) fever lasting for >14 days, (b) fever documented in the hospital, and (c) no cause identified after one week of routine investigations in the hospital.

Diagnostic considerations in febrile children at the time of presentation include:

- **Age of the child** is a major determinant for the risk for serious bacterial infections or occult bacteremia. Ranging from as high as 30% in newborns to <5% in older infants or toddlers, as follows:
  - A febrile newborn carries substantially high-risk of occult bacteremia (~30%) and serious bacterial infections (~7–10%), e.g. septicemia, meningitis, pneumonia or pyelonephritis, despite being apparently well clinically.
  - Post-neonatal young infants (1–3 months) with fever also have a substantial risk of occult bacteremia (10–15%), though not as high as in newborns. Localizing signs are often absent in these cases despite presence of serious bacterial infections. Many criteria have been developed to identify low-risk cases in this age group, e.g. Rochester criteria **(Table 10.1)** which has a negative predictive value of >98% for serious bacterial infection or bacteremia.
  - Fever in older infants and toddlers (3–36 months) is usually *viral* except in presence of (a) high fever 39°C, (b) leukocytosis 15,000 cells/mm^3 with neutrophilia, (c) elevated inflammatory markers, e.g. CRP, and (d) persistence beyond one week. Most of these cases have localizing signs and risk of occult bacteremia or SBI is < 5% in these cases, in absence of significant clinical abnormalities.
- **Duration of fever:** While short-duration fevers without focus are common and usually benign, persistent of fever beyond a week is a cause of concern and need detailed revaluation and investigations.
- **Periodicity of fever** is an important diagnostic clue in many febrile illnesses, as follows, though the course may be modified by antipyretics:
  - *Continuous fever* with diurnal variation of <0.5°C, e.g. in pneumonia, urinary tract infection, etc.
  - *Remittent fever* with diurnal variation of >1°C but never touching the baseline, e.g. in enteric fever (step-ladder pattern), infective endocarditis, etc.
  - *Intermittent fever* alternating with short afebrile periods, e.g. in malaria, kala-azar, viral fevers. In septicemia, child may never be absolutely afebrile but temperature variations often exceed 5°C.
  - *Relapsing or biphasic fever,* i.e. reappearance of fever after an afebrile period of >2–3 days, e.g. in dengue, leptospirosis, Hodgkin disease (Pel- Epstein fever), etc.
  - *Single isolated spikes* are usually benign, due to intravenous infusions, invasive procedures, drugs and vaccinations.
- **Severity of fever** may be divided into:
  - *Malignant hyperpyrexia* (>41°C), contrary to popular perception, is usually non-infective in origin, e.g. heat-stroke, pontine hemorrhage, drugs/poisonings, hypothalamic dysfunction, neuroleptic syndrome, etc.
  - *Moderate fever* (38–41°C) in most infectious illnesses.
  - *Low-grade fever* (<38°C) in TB, malignancies,viral infections, etc.
  - *Hypothermia* (<35°C) is an important indicator of serious infections in newborns and immunocompromised children.
  - *Significant mismatch between core and skin temperature* (>1°) indicates impending shock.
- **Circadian rhythm,** e.g. evening-rise temperature in tuberculosis or malignancies.
- **Inter-febrile clinical state:** Absence of ill-look between febrile episodes indicates viral etiology or malaria. In bacterial infections, child continues to betoxic or lethargic, even during afebrile phase.
- **Pattern of defervescence:**
  - *Sudden defervescence* (by *crisis*) with profuse sweating, e.g. malaria, roseola infantum.
  - *Gradual defervescence* over 48–72 hours (by *lysis*), e.g. enteric fever or other bacterial infections.
- **Presence of co-existing features:** For example,
  - *Chills and rigors* usually indicate—malaria, urinary tract infection, pneumococcal pneumonia, septicemia, amebic hepatitis, infective endocarditis.
  - *Bradycardia* is common in enteric fever, brucellosis and factitious fevers.
  - *Localizing signs,* e.g. rash (Ch 10.1.3), jaundice (hepatitis), lymphadenitis (viral infections, malignancy), altered sensorium or seizures (CNS infections), respiratory distress (respiratory infections), splenomegaly (malaria, kala-azar), dysuria (urinary tract infections), heart disease (infective endocarditis), osteo-articular pain (osteomyelitis, arthritis, rheumatic disorders), etc.

TABLE 10.1: Rochester criteria for low-risk of serious infection in children 1–3 months age

Apparently well infant with normal examination and

- Total leukocyte count 5000–15000 cells/mm^3 with absolute band cell count <1500 cells/mm^3
- Urine < 10 WBC/HPF
- Stool < 5 WBC/HPF (in presence of diarrhea)

– H/O vaccination, as fever is a common side effect of many vaccines given in this age group though rarely lasts for more than 24–48 hours. In an unwell child, fever should not be attributed to vaccination alone

Management of febrile child depends on the severity of the illness at the time of presentation, possible clinical diagnosis and underlying risk of occult bacteria or serious bacterial infections, apart from symptomatic antipyretic therapy.

Consensus Guidelines on Evaluation and Management of the Febrile Child presenting to the Emergency Department in India (2017) as well as *IAP standard treatment guidelines 2022* suggest that:

- **All febrile newborns** need hospitalization and complete investigative workup which includes complete blood count (CBC), C-reactive protein (CRP), peripheral blood smear (PS) (band form, toxic granules, vacuolization, immature/total ratio), blood and urine culture, urine analysis (UA), lumbar puncture (LP), and chest *X*-ray (CXR) is mandatory. Stool should be examined for pus cell and red blood cell (RBC) only if change in frequency of stool is present. First negative septic screen in an active febrile newborn is not the indication for discharge.

  All ill-appearing newborns should be started on empirical intravenous antibiotics immediately on hospitalization, including ampicillin (100–200 mg/kg/d q8hr) and gentamicin (7.5 mg/kg/d q8hr), after collection of cultures.
- **Young infants (1–3 months),** if apparently active except fever, should be observed in the emergency room, along with CBC, PS and urine analysis and culture (after catheterization) and blood culture in all cases. Chest X-ray is indicated if temperature 39ºC, leucocyte count 20,000/mm^3 or respiratory signs are present. Lumbar puncture is indicated only in sick-looking child.

  All sick-looking children of this age group should be hospitalized and started on empirical intravenous antibiotics immediately on hospitalization, including Ceftriaxone (100 mg/kg/d q12hr) or (75 mg/kg/d q12hr), dose depending on the presence or absence of meningeal involvement.

  Apparently well children of this age group should be managed symptomatically and may be hospitalized for observation or asked to follow-up after 24 hours, for further treatment, if required.
- **Children aged 3 months – 3 years** do not need urgent investigations, if apparently well and have no localizing signs, except urine microscopy, if have fever >24 hours and past history of UTI. However, sick-looking children of this age must be investigated with CBC, PS, urine analysis and culture, blood culture in all cases and chest skiagram and CSF in selected cases. Rapid tests for malaria, dengue and enteric fever may be done in endemic areas.

  While sick-looking children of this age group should be hospitalized and started on empirical intravenous Ceftriaxone, other apparently well children may be managed symptomatically with follow-up after 24 hours, for further treatment, if required.
- **Febrile children >3 years** are unlikely to have serious bacterial infections in absence of thelocalizing signs and need detailed workup only in presence of: (a) prolonged pyrexia, (b) immunocompromised state, (c) co-morbidities, or (d) nosocomial risk factors. Investigations in these cases should directed on clinical suspicion, though rapid tests for malaria, dengue and enteric fever may be done in endemic areas. Treatment is these cases should be directed on clinical grounds.

Antipyretic therapy includes: *(a) hydrotherapy*, i.e. tepid water sponging to bring down high fever, and *(b) pharmacotherapy.* Paracetamol (PO10–15 mg/kg/dose) is the safest antipyretic in children, though others, e.g. Ibuprofen (PO 5–10 mg/kg) or Mefenamic acid (PO 5–7 mg/kg) may be used in selected cases. IV paracetamol may be given in babies with intractable vomiting or altered senosrium as 7.5 mg/kg (<10 kg) or 15 mg/kg in children >10 kg. Nimesulide and Aspirin are not recommended as antipyretics in children due to potential risk of hepatotoxicity and Reye's syndrome, respectively. No antipyretics are necessary in low-grade fevers <38°C.

10.1.2 PYREXIA OF UNKNOWN ORIGIN (PROLONGED PYREXIA)

Pyrexia of unknown origin (PUO) is defined as any fever fulfilling following criteria:

- Fever of >14 days duration,
- Fever documented in the hospital,
- Cause remains unidentified even after one week of routine investigations in the hospital.

Etiology: PUO usually indicates presence of a chronic infection, immunological disorder or malignancy **(Table 10.2)**. Infections account for more than half of these cases and *five* commonest causes in Indian children are: (a) enteric fever, (b) malaria, (c) tuberculosis, (d) urinary tract infection, and (e) infective hepatitis. In ~30%, diagnosis remains an enigma despite best laboratory support. Rheumatic disorders (~10%) and malignancies (~5%) are emerging as important causes of PUO after easier availability of diagnostic tests for common infections.

Diagnostic approach in prolonged pyrexia depends on: (a) epidemiological risk of diseases in local population, (b) review of case history, including prior medications and investigations, (c) re-assessment of clinical examination for missed/new findings and (d) baseline and

TABLE 10.2: Causes of prolonged pyrexia (PUO) in children

Infectious causes	*Non-infectious causes*
1. Bacterial	***1. Immunological***
Enteric fever	Rheumatic fever
Urinary tract infection	Collagen disorders: JRA, SLE
Infective endocarditis	Chronic active hepatitis
Brucellosis	Chronic inflammatory bowel diseases
Deep-seated abscess	
Bone/joint infection	***2. Neoplasms***
2. Viral	Leukemia
Viral hepatitis	Lymphoma
HIV	Solid tumors
Infectious mononucleosis	***3. Neurological***
3. Parasitic	Autonomic disorders*
Malaria	Hypothalamic lesions
Amebic hepatitis	***4. Endocrinal***
4. Miscellaneous	Hyperthyroidism
Leptospirosis	Diabetes insipidus
Rickettsial fevers	***5. Miscellaneous***
Opportunistic Infections	Fictitious fever
	Drug fever

*e.g. Riley-Day syndrome

relevant investigations, as dictated by clinical suspicion **(Table 10.3)**.

Management: Since many cases of PUO are non-infectious in origin, empirical antibiotics are not recommended and may obscure the diagnosis. Treatment is largely supportive and empirical trials, e.g. antitubercular therapy should be avoided.

10.1.3 EXANTHEMATOUS FEVERS (Fever with Rash)

While rashes are seen in many febrile illnesses, term *Exanthematous fevers* is usually reserved for *fevers consistently associated with skin eruptions* during the usual clinical course.

Etiology: Skin lesions in infectious diseases may be due to: (a) direct inoculation, e.g. anthrax, (b) contagious spread from adjacent foci, e.g. herpes, (c) hematogenous spread, e.g. meningococci, (d) toxins, e.g. scarlet fever and (e) immune reactions, e.g. rheumatic fever. Most exanthematous fevers are viral in origin **(Table 10.4)**, commonest being measles and varicella.

Diagnostic evaluation of exanthematous fevers depends on the epidemiological history of similar illnesses in the community, along with: (a) duration and severity of prodromal phase, (b) nature, distribution and duration of rash and (c) other associated features **(Table 10.5)**. Non-infective causes of maculopapular or Vesiculobullous rashes (*see* Ch25.5 and 25.6) should also be excluded.

TABLE 10.3: Laboratory investigations in PUO

- **Baseline** *(in all prolonged pyrexia)*
  - Complete hemogram
  - Peripheral smear for immature cells, parasites
  - Urine analysis
  - X-ray chest and sinuses
  - Tuberculin test
  - Widal test
- **Second-line** *(in all PUO cases)*
  - *Biochemical:* Liver function tests
  - *Microbial:* Blood/urine cultures, AFB
  - *Cytological:* CSF, bone marrow
  - *Serological:*
    - *Infections:* HIV, leptospira, brucella
    - *Others:* ASO, ANA titers
  - *USG abdomen for* deep-seated abscess
  - *Echocardiography for* infective endocarditis
- **Third-line** *(in selected cases)*
  - Whole body CT/MRI
  - Radionuclide scans (bones, abdomen)

TABLE 10.4: Exanthematous fevers in India

- **Viral:**
  - *Common:* Measles, varicella, enterovirus, dengue
  - *Others:* IM, roseola, E. infectiosum, arboviruses
- **Bacterial:**
  - *Common:* Enteric fever, meningococcemia
  - *Uncommon:* Scarlet fever, anthrax
- **Spirochetal:** Leptospirosis
- **Rickettsial:** Typhus, rickettsial pox
- **Mycoplasma:** *M. pneumoniae*
- **Protozoal:** Toxoplasmosis
- **Immunological:** Rh. fever, JRA, Kawasaki disease
- **Drug reactions:** Stevens-Johnson syndrome

IM: Infectious mononucleosis; **JRA:** Juvenile rheumatoid arthritis

10.1.4 HEMORRHAGIC FEVERS (Fever with Petechiae/Purpura)

Fever with petechial/purpuric lesions indicates serious life-threatening infections, often associated with bacteremia, sepsis and meningitis. Common causes of hemorrhagic fevers in Indian children, excluding co-existing bleeding disorders, are as follows:

- *Viral fevers*
  - Dengue (DHS/DSS)
  - *Other arboviruses:* Chikungunya, West-Nile virus, Kyasanur Forest disease
  - Non-polio enteroviral infections
  - Hemorrhagic measles or chickenpox
- *Bacterial infections*
  - Meningococcemia,
  - *Others:* Anthrax, DIC
- *Spirochetal infections:*
  - Leptospirosis

TABLE 10.5: D/D of rash in common exanthematous fevers

Illness	*Rash characteristics*				
	Day[1]	*Type*[2]	*Distribution*[3]	*Duration*[4]	*Important prodromal/coexistent features*
Measles	4–5th	Maculopapular	Hairline > GEN	5–7 d	Fever, conjunctivitis, koplik spots, Post-measles staining on recovery
Rubella	5–7th	Macular flush	Face > GEN	2–3 d	Mild fever, lymphadenopathy
Chickenpox	2nd	Pleomorphic	Centripetal	7–10 d	Transient fever
E. subitum (Roseola)	5th	Discrete macular Rose-colored	Trunk > GEN	1–3 d	High fever for 3–5 days, *Rash appears after fever disappears*
E. infectiosum (Fifth disease)	–	Macular flush *(Slapped-cheek)*	Trunk> GEN	10–14 d	Mild fever Fever, absence of catarrh
Dengue	1–2nd	Macular flush	GEN	2–3 d	Mild fever
Enteroviral illness	1–2nd	Maculopapular	GEN	2–3 d	Fever, circumoral pallor, with flush face, *pastia lines*
Scarlet fever	2nd	Punctate macular *(Goose-flesh)*	Flexural > GEN	5–7 d	Fever with shock/meningitis
Meningococci	1–2nd	Purpuric	GEN	–	Fever, toxic, hepatosplenomegaly
Enteric fever	7th	Maculopapular (Rose-spots)	Truncal	3–5 d	Fever, local eshar, lymphadenopathy
Rickettsial infections	3–5th	Maculopapular	Limbs > GEN	2–4 weeks	Fever, lymphadenopathy, conjunctivitis, strawberry tongue, desquamation of palm/soles
Kawasaki disease	1st week	E. multiforme	Truncal, Groin	1–3 weeks	

GEN: Generalized
[1]usual day of appearance of rash, may vary. A simpler way to remember the day of appearance of rash is to remember a mnemonic – *'Very Sick Patient Must Take Rest' - Varicella* (1 day), *Scarlet fever* (2 days), *Pox i.e.* small *pox* (3 days), *Measles* (4 days), *Typhus* (5 days) and *Rubella* (6 days).
[2]Usual appearance, may vary, special appearance in parentheses
[3]Usual distribution and progression (>) from the site of first appearance
[4]Usual disappearance of primary rash, secondary lesions, e.g. staining (measles), scars (chickenpox), desquamation (scarlet fever, Kawasaki disease) may persist for 2–4 weeks.

- Rickettsial fevers
- *Others:* Purpura fulminans

All fevers with petechial/purpuric rash need hospitalization and close supervision for signs of internal bleeding, e.g. hematemesis, hematuria, etc. Some important hemorrhagic fevers are discussed later in relevant chapters.

10.1.5 FEBRILE NEUTROPENIA (Fever in a Neutropenic Child)

Fever in a neutropenic child is an emergency that needs urgent evaluation and institution of empirical antibiotic therapy, without waiting for a diagnosis.

Febrile neutropenia (FN) is generally defined as:

- Single oral temperature > 38.3°C (101°F)% or > 38°C sustained for > 1 hour,
- Absolute neutrophil count (ANC) < 500/mm^3 or expected to drop below this level in next 24 hours.

Development of fever in a case with neutropenia due to any cause indicates possibility of serious underlying infections, though clinical signs may be masked due to paucity of inflammatory response. Risk of bacterial infection is inversely related to absolute neutrophil count.

Microbiologically, predominant infections in neutropenic children are bacterial, including *Staph. aureus* (~50%), *Pseudomonas* (~20%) and *anaerobic infections* (~15%). While opportunistic viral, (e.g. CMV) and fungal infections are also common in these cases due to co-existing immunological defects, children with *isolated neutropenia* are not excessively prone to these infections.

Clinical presentation of infections in neutropenic children is directly related to its severity:

- *Mild neutropenia* with absolute neurtrophil count >1000/mm^3, is generally well tolerated.
- *Moderate neutropenia* (500–1000 cells/mm^3), may be asymptomatic or presents with mucositis, sinopulmonary infections, fulminant skin/soft tissue infections and enterocolitis.
- *Severe neutropenia* (<500 cell/mm^3) is frequently associated with generalized and potentially fatal infections, e.g. septicemia, pneumonia and visceral abscesses. *Meningitis is unusual* in neutropenic patients.

Disproportionately *less signs of inflammation with minimal pus formation is* an important feature of sepsis in neutropenic cases. Child should be thoroughly examined for source of infection, specially for venous access sites and mucosal surfaces.

Diagnosis of infection in FN depends on microbial cultures from blood and potential sites for entry of infection, e.g. catheters or central lines. Serial neutrophil counts and inflammatory markers, e.g. CRP are necessary to assess the course of disease, along with investigation to search for focus of infection, e.g. chest skiagram, urine analysis, etc. and biochemical investigations for organ dysfunction.

Management aims to recognize infection in early stages and prevent rapid progression from bacteremia to septicemia to septic shock. Important steps include:

- **Risk-assessment:** All cases of FN must be classified as *high-risk* or *low-risk* for serious infections before deciding the line of management **(Table 10.6)**.
- **Management of high-risk FN:** Children with high-risk FN need immediate hospitalization and initiation of empirical antibiotics within 60 minutes, without waiting for reports. Choice of *empirical antibiotic therapy* in them must include a broad-spectrum beta-lactam antibiotic with anti-pseudomonal cover, e.g. *piperacillin-tazobactam* (IV 300 mg/kg/day q8hr) or a fourth-generation cephalosporin, e.g. *cefepime with/without tazobactam* (IV 100 mg/kg/day q12hr) or a carbapenem, e.g. *meropenem* (120 mg/kg/day q8hr). Vancomycin (IV 45–60 mg/kg/day q8hr) must be added in clinically unstable patients with hypotension/shock or in those with (a) mucositis, (b) skin and soft-tissue infection, (c) central lines, (d) locally high MRSA prevalence.

  These cases, specially if on steroids, should also be investigated for invasive fungal disease (IFD) and started on empirical antifungal therapy if fever persists for >96 hours with *liposomal amphotericin B* (IV 3–5 mg/kg/day) or *Caspofungin* (IV 70 mg/m^2 on day 1 followed by 50 mg/m^2/day) empirical antifungal therapy may be stopped after resolution of fever, provided there is no feature suggestive of IFD.

TABLE 10.6: Risk-stratification in febrile neutropenia

	High-risk	*Low-risk*
Duration	>10 days	<10 days
ANC count	<100 cells/mm^3	>500 cells/mm^3
Primary disease	Leukemia/NHL	Solid tumors
Course of disease	Relapse/refractory	No relapse/refractory
Treatment	HSCT	Chemotherapy
Risk factors*	Present	Absent

*Hypotension, Hypoxia, Altered sensorium, Respiratory distress, Mucositis or Abdominal symptoms
HSCT: Hematopoietic stem cell transplant

- **Management of low-risk FN:** Low-risk FN may be treated on OPD basis with oral antibiotics, if patient is accepting well and can be monitored at home. Initial choice of antibiotics in these cases include a fluoroquinolone, e.g. ciprofloxacin (PO 20–30 mg/kg/d q12hr) alone or in combination with amoxicillin-clavulanate (50–80 mg/kg/d q12hr). Same antibiotics may be given parenterally in a small child, vomiting or lack of compliance, after hospitalization.
- **Supportive measures** includes:
  - Barrier nursing, hand hygiene, and strict asepsis.
  - Nutritional support, either enteral with nasogastric tube, or parenteral, as required.
  - Transfusions to maintain hemoglobin >8 g/dl and platelet count >20,000/mm^3.
  - Treatment of primary causes along with recombinant G-CSF therapy in severe/persistent neutropenia (Ch 19.8).
  - Adequate pain relief with opioids should be provided for mucositis, colitis, evolving abscess, or fissures. Paracetamol should be avoided in a FN child until it is clear that the criteria for starting antibiotics are fulfilled.
- **How long to treat?** Antibiotic therapy should continue till the patient is afebrile for at least 48 hours, neutrophil counts rise >500 cells/mm^3 and blood culture is sterile. Persistent of fever alone does not warrant change of antibiotics, which should be changed as per culture reports or in cases developing hemodynamic instability, fresh focus of infection or increase in inflammatory markers.

10.1.6 DRUG FEVER

Drug fever is an uncommon but important cause of prolonged fever, defined as:

- Unexplained pyrexia during the course of specific drug therapy, and
- Normalization of temperature within one week of discontinuation of offending drug.

Clinical indicators: Drug fever is a diagnosis of exclusion, though following characteristics are strongly suggestive:

- Onset of fever within 24–48 hours of starting the offending drug,
- Low-grade persistent fever, rarely exceeding 39°C,
- Frequently, but not essentially, associated features, e.g. rash or eosinophilia,
- Disappearance of fever within 7 days of stopping the suspected drug,
- Reappearance of fever after re-instituting same drug.

Mechanisms: Although frequently idiopathic, possible mechanisms in drug fever include:

- *Presence of exogenous pyrogens* in the preparation, e.g. IV amphotericin.

- *Release of endogenous pyrogens* due to specific drug action, e.g. antibiotics, cytotoxic agents.
- *Inherent pharmacological action* like reduced sweating, e.g. atropine or antihistaminics.
- *Allergic response*, e.g. sulpha-drugs or penicillin.
- *Idiosyncratic reaction* ? genetic predisposition for qualitative intolerance other than immunological mechanisms, e.g. quinine or sulpha drugs.

Management: No treatment is indicated except discontinuation of the suspected drug, though symptomatic therapy may be used if the offending drug cannot be discontinued for medical reasons.

10.2 STAPHYLOCOCCAL INFECTIONS

Staphylococci are broadly classified as coagulase positive (*Staph. aureus*) or coagulase negative (*Staph. epidermidis*), based on their ability to produce a clumping factor (coagulase) to protect themselves against host defense. *Staph. aureus* is a common colonizing pathogen in nasopharynx with carrier rate of 20–30%, transmitted as a droplet infection. All colonized children are not symptomatic and development of disease depends on strain-virulence and host-susceptibility.

High-risk factors for staphylococcal disease include: (a) impaired skin/mucosal barrier, e.g. trauma, surgery, burns, vascular access, shunts, (b) altered nasal flora after viral infections or prolonged antibiotics, and (c) immunodeficiency states.

Pathogenesis: Disease may result due to direct tissue invasion (localized disease) or via toxins produced by different strains, e.g. exfoliative toxins (*staphylococcal scalded skin syndrome*), enterotoxins (*food poisoning*), and TSS-1 (*toxic shock syndrome*).

Clinical spectrum: Staphylococci is the leading cause of superficial skin infections in children, apart from various localized or generalized serious infections **(Table 10.7)**.

Diagnosis rests on the culture from infected lesion. A positive skin/nasopharyngeal culture is of a little significance due to normal colonization.

TABLE 10.7: Clinical spectrum of staphylococcal infections

- **Skin infections**
  - *Focal:* Impetigo, folliculitis, wound infection
  - Staphylococcal scalded skin syndrome
- **Respiratory infections**
  - *Upper*:* Otitis, sinusitis, bacterial tracheitis
  - *Lower:* Pneumonia, empyema, pneumothorax
- **Septicemia**
- **Metastatic lesions:**
  - *Osteoarticular:* osteomyelitis, arthritis
  - *CNS:* Meningitis, brain abscess, epidural abscess
  - *GIT:* Peritonitis, food poisoning
  - *Heart:* Pericarditis, endocarditis
  - *Kidney*:* Renal/perinephric abscess
  - *Muscles:* Tropical myositis and muscle abscesses

*Tonsilopharyngitis and UTI is rare

Treatment includes specific antibiotic therapy and drainage of pus. Antibiotic of choice is a penicillinase-resistant, semisynthetic penicillin, e.g. *cloxacillin* or *amoxycillin-clavulanic acid*, while penicillin-allergic or resistant cases should be treated with *vancomycin* or *imipenem*.

Methicillin-resistant Staph. aureus (MRSA) is an emerging problem in critically sick children, due to presence of a penicillin-binding protein, which is relatively resistant to β-lactam ring of antibiotics. Although methicillin is currently not available, the term 'MRSA' continues to be in use to denote organisms resistant to cloxacillin and other semisynthetic penicillins.

Prevention of staphylococcal infections in hospital requires: (a) strict hand-washing, with/without chlorhexidine, (b) isolation of case or carrier, and (c) rational use of antibiotics.

Toxic-shock syndrome (TSS) is an acute multi-systemic disease due to an exotoxin TSS-1, usually caused by staphylococci phage type-I. Mostly seen in menstruating women due to use of infected tampoons, non-menstrual TSS has been reported following wound infection, nasal packing for epistaxis and invasive staphylococcal disease.

Clinically TSS is characterized by three *major* features: (i) sudden onset of high fever, (ii) severe hypotension/shock and (iii) generalized erythematous rash after 24 hours of the onset of fever.

Important *minor* features include—(a) mucosal lesions, e.g. strawberry tongue, conjunctival congestion, (b) vomiting/diarrhea, (c) severe myalgia, (d) altered sensorium without focal signs, (e) liver/renal abnormalities, and (f) thrombocytopenia.

Diagnosis depends on presence of *all major criteria and/or minimum three minor criteria* (mentioned above), after exclusion of other causes and negative blood culture. *D/D* includes streptococcal TSS and Kawasaki disease.

Treatment includes drainage of infected site, parenteral antibiotic therapy with vancomycin, and supportive treatment for shock and other complications.

Prognosis is poor in untreated cases. Appropriately treated cases recover in 7–10 days, *leaving behind a desquamating lesion, especially over palm and soles*.

Other staphylococcal disorders, staphylococcal scalded skin syndrome (SSSS) are discussed elsewhere (Ch25.6).

Coagulase negative staphylococci (CONS), i.e. *Staph. epidermidis*, is a normal inhabitant of human skin, oropharynx and genital tract. Originally thought to be non-virulent, it is now known to cause serious nosocomial infections in susceptible children.

High-risk factors for CONS infections include: (a) presence of indwelling devices, e.g. shunts, catheters or prosthetic devices, etc., (b) post-operative infections, and (c) immunocompromised states.

Clinical spectrum: CONS infections may be limited to occult bacteremia or present with site-related infections, e.g. CSF-shunt infection (commonest cause), urinary catheter-related UTI, dialysis catheter-related peritonitis or infective endocarditis in cases with prosthetic valves.

Diagnosis rests on blood or shunt/catheter-tip culture, but should be differentiated from normal colonization. A CONS culture is considered as pathogenic if: (a) at least two cultures from same site at different times or different sites at same time are positive, *or* (b) patient is high-risk, i.e. newborn or has an *in situ* catheter.

Treatment: Vancomycin is the drug of choice for CONS, though the efficacy may be enhanced with addition of rifampicin or an aminoglycoside. Removal of suspected source, e.g. catheter is essential.

10.3 STREPTOCOCCAL INFECTIONS

Streptococci are classified according to their hemolytic properties (α, β, γ) *or* carbohydrate components in the cell wall (Group A-H, K-V).

Group A β-hemolytic streptococci (GAβHS) is a common colonizer of oropharynx in normal children (~20%), acquired as droplet infection from infected/colonized persons.

Pathogenesis: After infection, GAβHS attach to oropharyngeal mucosa to produce many *extra-cellular toxins*, (e.g. pyrogenic exotoxin, streptolysin O and S) for systemic manifestations and *digestive enzymes*, (e.g. streptokinase, hyaluronidase, DNAse-B) to facilitate the local spread. GAβHS disease in children represents: (a) local spread, (b) distant spread via bacteremia, (c) toxin-mediated injury, or (d) immunological injury.

High-risk factors for GAβHS infection or colonization include: (a) school-age children, (b) overcrowding, (c) winter season (except by nephritogenic strains, common in summer season).

Clinical spectrum of GAβHS disease spans from localized skin/respiratory disease to systemic disease, e.g. rheumatic fever or acute nephritis **(Table 10.8)**.

TABLE 10.8: Clinical spectrum of GAβHS infections

Direct spread:
- *URTI:* Tonsillopharyngitis, otitis, sinusitis
- *LRTI:* Pneumonia, pleural effusion
- *Skin:* Impetigo, erysipelas, cellulitis, fasciitis
- *Genital:* Vulvovaginitis in pre-pubertal girls

Hematogenous spread: *(metastatic lesions)*
- *CNS:* Meningitis, brain abscess
- *Bones and joints:* Arthritis, osteomyelitis
- *GIT:* Peritonitis, brain abscess

Toxin mediated:
- Scarlet fever
- Streptococcal toxic shock-like syndrome (TSS)

Immunological injury:
- Rheumatic fever
- Acute glomerulonephritis

Diagnosis depends on throat culture in symptomatic case. Positive throat culture in an asymptomatic child is not necessarily pathogenic and reflects colonization. A serological test-elevated *anti-streptolysin O* (ASO) titers (>200 todd units and rising) is commonly used indicator of recent streptococcal infection. Other serological tests include elevated *anti-DNAase B* and *anti-hyaluronidase* titers, which are more specific and *anti-streptozyme* test, which is most sensitive and detects presence of extracellular streptococcal antigens.

Treatment: *Penicillin* is the drug of choice, given orally or parenterally for minimum 10 days. In allergic individuals, erythromycin, clindamycin or first-generation cephalosporins may be used as alternatives.

Prevention: No vaccine is available for clinical use and prophylaxis with long-acting penicillin is recommended only in rheumatic fever.

Scarlet fever, rarely diagnosed in Indian children, is caused by a pyrogenic exotoxin (A, B, C), released by select strains of GAβHS.

Clinically, it is characterized by: (a) sudden onset of high fever and sore-throat, (b) typical *scarlatiniform* rash–a generalized red, punctate exanthem after 24–48 hours of fever that begins from axilla, groin and neck and better felt than visible (*goose-flesh or sand-paper skin texture*), and (c) circumoral pallor, flushed face and *pastia lines* (hyperpigmented creases in ante-cubital fossae). Fever subsides spontaneously after 5–7 days, followed by gradual desquamation of rash.

Poststreptococcal reactive arthritis (PSRA) denotes onset of acute arthritis following an episode of GAβHS pharyngitis, not fulfilling the Jones criteria for rheumatic fever. It is unclear whether this entity represents a distinct syndrome or a variant of rheumatic fever. Unlike rheumatic fever, PSRA may also involve small peripheral joints and axial skeleton, and is typically non-migratory. ASO titres are elevated.

Response to NSAIDs is usually unsatisfactory. Valvular disease is rare but follow-up is recommended for 1–2 years along with secondary penicillin prophylaxis in some cases.

Pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus pyogenes* (PANDAS) denotes a group of neuropsychiatric disorders, e.g. obsessive-compulsive disorder or tics, with a possible relationship with GAβHS infection-induced autoimmune antibodies that cross-react with brain tissue. Causal relationship is not yet proven and penicillin prophylaxis or immune-regulatory therapy to treat exacerbations is not recommended.

Group B streptococci (GBS) is a normal inhabitant of maternal genital tract and gastrointestinal tract, not associated with any major illness *except* in newborns. While GBS is the *commonest cause of early neonatal sepsis/*

meningitis in western countries due to the transvaginal infection during delivery, it is either uncommon or rarely documented in Indian newborns. Penicillin with an aminoglycoside is the drug of choice in these cases.

α-hemolytic streptococci, (e.g. *S. viridans*) is a part of normal skin and oropharyngeal flora. While rarely pathogenic in normal children, it is the commonest cause of infective endocarditis in cases with heart disease. Drug of choice is ampicillin with an aminoglycoside agent.

Group D streptococci, now re-classified as 'Enterococci' (*E. faecalis* and others), are common inhabitants of oropharynx and gastrointestinal tract. These organisms, previously considered as nonpathogenic, are emerging as important *nosocomial pathogens* in wound infections, catheter-related sepsis, urinary tract infections and infective endocarditis. Penicillin is generally *not effective* and drug of choice is ampicillin with an aminoglycoside *or* vancomycin.

Vancomycin-resistant enterococci (VRE), an emerging problem in recent years, may be treated with linezolid or other newer antibiotics, e.g. daptomycin or tigecycline. Timely removal of urinary and vascular catheters and debridement of necrotic tissue are important strategies to prevent enterococcal infections.

10.4 PNEUMOCOCCAL INFECTIONS

Streptococcus pneumoniae is a common colonizing organism of upper respiratory tract, present in encapsulated and noncapsulated forms. Only capsulated forms are pathogenic and classified according to their type-specific capsular polysaccharide. Human disease is usually caused by serotypes 4, 6, 9, 14, 19 and 23.

Pathogenesis: Pneumococcal colonization is common in under-five children, institutionalized cases and during winter season, via droplet infection from a case/carrier. Although host-defence mechanisms, e.g. mucociliary clearance and local phagocytosis limit the infection to colonized site, it may spread in susceptible host to neighboring tissues (localized disease) or via bacteremia to distant tissues (invasive disease).

High-risk factors for pneumococcal disease include: (a) impaired mucociliary clearance due to viral infections, passive smoking and airway allergy, or (b) immunodeficiency states, *specially with impaired splenic function*, e.g. sickle cell disease, asplenia, splenectomy, etc.

Clinical spectrum spans from local upper respiratory tract disease to invasive disease, e.g. meningitis, pneumonia, etc. **(Table 10.9)**. *Pneumococci is the leading cause of community-acquired pneumonia, otitis media and meningitis in 1–5 years age group.*

Diagnosis rests on culture from the site of infection or blood. Nasal/pharyngeal culture isolation is of little significance, due to frequent colonization.

TABLE 10.9: Clinical spectrum of pneumococcal infections

Direct spread:
- *URTI:* Otitis media, sinusitis, pharyngitis, croup
- *LRTI:* Pneumonia, pleural effusion

Hematogenous spread:
- *CNS:* Meningitis, epidural abscess, brain abscess
- *Bones and joints:* Arthritis, osteomyelitis
- *Cardiac:* Pericarditis, myocarditis
- *GIT:* Peritonitis

Immunological mechanisms
- Hemolytic-uremic syndrome
- Disseminated Intravascular Coagulation (DIC)

Treatment: *Penicillin* is the drug of choice in susceptible cases, while resistant or allergic cases must be treated with cefotaxime or ceftriaxone with/without vancomycin. Rifampicin (PO 20 mg/kg BD) may be added in severe, non-responsive cases.

Prevention of pneumococcal disease involves universal immunization of all children with polyvalent conjugated vaccine (PCV). NIS recommended three doses of PCV_{10} in all infants at the age of 6 weeks, 14 weeks and 9 months. IAP recommends three primary doses of $PCV_{10/13}$ at 6,10 and 14 weeks followed by a booster dose at 12–15 months of age (See Ch 9.2.1).

Additionally, all high-risk cases with (a) splenic dysfunction, e.g. asplenia, splenectomy or sickle cell disease, (b) nephrotic syndrome, (c) CSF leaks, (d) HIV/AIDS, and (e) chronic cardiopulmonary disease, etc. should also receive 23-valent polysaccharide vaccines (PPSV) after two years of age or before surgery (splenectomy, cochlear implant), etc. PPSV is not adequately immunogenic below 2 years of age and need to be repeated after 3–5 years.

Penicillin prophylaxis with 3-weekly IM benzathine penicillin or daily PO penicillin is also recommended in splenectomized children against pneumococcal infections, for at least 2 years after surgery.

10.5 DIPHTHERIA

Diphtheria is a life-threatening but vaccine preventable disease of childhood, characterized by acute severe inflammation of upper respiratory epithelium with membrane formation and marked toxemia. Incidence has declined in recent years, due to expanding immunization.

However, India still contributes to more than half of the cases of diphtheria globally and recent years have seen its resurgence in some geographical regions.

Epidemiology: Diphtheria is caused by three toxigenic strains (*gravis, intermedius and mitis)* of *C. diphtheria* (Klebs-Löffler bacillus)-gram positive non-invasive bacilli, almost exclusively found at respiratory mucous membranes of clinical cases or asymptomatic carriers.

Infection is usually transmitted as droplet infection or via contaminated fomites/dust, though direct contact with infected secretions is a rare source of infection.

Infectivity period lasts for ~2–4 weeks from the onset of disease, except in chronic carriers (>1 month). A case or carrier is considered as non-infective, only when at least two throat cultures at 24-hour interval are negative.

Diphtheria is most common in preschool children (<5 years), during autumn and winter season and unvaccinated children living in overcrowded environment.

Pathogenesis: Major virulence of the organism lies in its ability to produce an *exotoxin*, responsible for local necrosis and systemic complications. On entry, *C. diphtheriae* proliferates superficially at the site of inoculation (usually respiratory epithelium) to produce dense necrotic material consisting of organisms, epithelial cells, fibrin, leukocytes and erythrocytes and an adherent *grayish-white pseudomembrane that bleeds on attempted removal*.

Clinical features: After *incubation period* of 2–5 days, these cases present with

- ***Constitutional symptoms***, e.g. acute onset of moderate fever, typical toxic look and altered mental state, e.g. confusion or irritability. Circulatory collapse is not uncommon.
- ***Local respiratory tract symptoms,*** depending on the site of lesion, as follows:
  - *Pharyngotonsillar diphtheria*, the commonest type, presents with sore throat, dysphagia, submandibular swelling (*bull-neck*) and a grayish-white dirty membrane on soft palate, tonsils and pharyngeal wall that bleeds on removal **(Fig. 10.1)**.
  - *Laryngotracheal diphtheria*, the most serious type, presents with acute hoarseness of voice, croupy cough, stridor and progressive respiratory distress due to airway obstruction by membrane and tissue edema.
  - *Nasal diphtheria*, the mildest form, is characterized by serosanguineous or blood-mixed nasal discharge with membrane formation and shallow ulcers at nasal mucosa and external nares.
- ***Non-respiratory disease*** is uncommon, presenting as *cutaneous diphtheria* (punched-out, tender ulcers with membrane), *conjunctival diphtheria* (purulent/ulcerative conjunctivitis), *aural diphtheria* (otitis externa) and *genital diphtheria* (purulent or ulcerative vulvovaginitis).

Complications may be due to: (a) airway obstruction by membrane or edema, (b) aspiration of infected material, (c) exotoxin production, and (d) abnormal immune response, e.g. Guillain-Barré syndrome **(Table 10.10)**.

Airway obstruction is the immediate cause of mortality in most cases of diphtheria, though important late complications include:

- *Toxic myocarditis*, usually during 2nd week of illness presenting with tachycardia, muffled heart sounds, CCF and arrhythmia. Seen in 10–25% cases, it is responsible for ~ 50–60% of late deaths in diphtheria.
- *Cranial nerve palsies* usually present as *palatal palsy* in 2nd-3rd weeks with nasal twang, regurgitation of feeds and aspiration, or *occular palsies* in 3rd–5th weeks with loss of accommodation (earliest sign), blurred vision and squint.
- *Post-diphtheritic peripheral neuropathy* may be sensory, motor or combined, involves one or more limbs and usually develop in 2nd–3rd weeks.
- *Guillain-Barré syndrome* is a rare late complication after 6–8 weeks and indicates immunological insult.

Diagnosis of diphtheria depends on:

- *Clinical* presence of tough dirty-white membrane in throat that bleeds on removal,
- *Direct microscopy* of throat/nasal swabs with *Albert's stain* to demonstrate the characteristic club-shaped

Fig. 10.1: **Diphtheria (oropharyngeal membrane).**

TABLE 10.10: Complications of diphtheria

Respiratory:
- Airway obstruction > respiratory failure
- Secondary bacterial pneumonia
- Atelectasis
- *Late:* Bronchiectasis, lung abscess

Cardiac:
- Toxic myocarditis and CCF
- Endocarditis (extremely rare)

Neuropathies:
- *Cranial:* Palatal or ocular palsy
- *Peripheral:* Monoparesis
- Guillain-Barré syndrome

Renal:
- Proteinuria (secondary nephrotic syndrome)
- Acute renal failure

Others: Septicemia, hepatitis, arthritis

bacilli with metachromatic staining, arranged in a *chinese-letter pattern.* Fluorescent antibody staining is more sensitive for this purpose.

- *Throat/nasal swab culture* on Loffler or tellurite media to confirm the diagnosis and differentiate from *diphtheroids*—non-pathogenic oropharyngeal commensals.
- A rapid ELISA test, PCR test or modified Elk test may be used to detect presence of diphtheria toxin.
- *Ancillary investigations*, e.g. ECG, urine examination, etc. help to exclude complications.

D/D depends on the site of lesion:

- *D/D nasal diphtheria*: Other causes of serosanguineous or blood-mixed discharge, e.g. (a) viral rhinitis, (b) foreign body and (c) snuffles (congenital syphilis).
- *D/D pharyngotonsillar diphtheria*: Other causes of throat membrane, e.g. (a) streptococcal membranous tonsillitis, (b) viral membranous tonsillitis, e.g. infectious mononucleosis, (c) oropharyngeal candidiasis, (d) post tonsillectomy membrane.
- *D/D laryngeal diphtheria*: Other causes of acute croup and stridor (*see* **Table 16.8)**.

Management: Considering high mortality, morbidity and infectivity, all suspected cases of diphtheria need hospitalization. Important steps in management include:

- ***Strict isolation*** till at least two consecutive nose/throat swabs at 24-hour interval are negative.
- ***Specific anti-toxin therapy*** to neutralize free circulating toxin, given as early as possible.

  Currently, only equine diphtheria antitoxin (ADS) is available. Doses are empirical, depending on the site of membrane and duration of illness, i.e. 40,000-60,000 *IU for nasopharyngeal lesions, 20,000–40,000 IU for pharyngeal or laryngeal lesions of <48 hours and 80,000–1,20,000 IU for severe airway obstruction or longer illness.* It is given as slow IV infusion over 30–60 minutes after a subcutaneous test dose (0.02 ml) to detect hypersensitivity.
- ***Antibiotic therapy*** to stop further toxin production and eliminate organisms. Drug of choice is *Crystalline penicillin* (IV 1–1.5 lac U/kg/d q6hr) or Erythromycin (PO 40–50 mg/kg/d q6hr), given for 14 days or till two successive cultures are negative. However, antibiotic therapy is not a substitute for antitoxin therapy.
- ***Management of complications:*** Immediate tracheostomy is indicated in severe respiratory distress. Even in mild cases, hospitalization with complete bed rest is indicated for 2 weeks—to monitor for late complications, to reduce risk of myocarditis and to prevent spread of infection.

Prevention: Diphtheria is preventable by:

- ***Active immunization*** of all children with three primary doses at 6, 10 and 14 weeks of age and two boosters at 18 months and 5 years, followed by Td every 10 years from 10 years onwards (*see* Ch 9.2.1). IAP also recommends a single dose of Tdap vaccine after 7 years, followed by Td at 17–18 years.
- ***Isolation and treatment*** of symptomatic cases as well as asymptomatic carriers. All carriers must be treated with PO Erythromycin (40–50 mg/kg/d q6hr) for 10–14 days or till two throat-cultures are negative. ADS is not required in asymptomatic cases, even if culture is positive.
- ***Management of close contacts:*** While all close contacts should be cultured from nasopharynx to detect asymptomatic carriers, chemoprophylaxis with PO Erythromycin (40–50 mg/kg/day for 7–10 days) or a single IM Benzathine Penicillin 6 Lac IU (12 Lac IU above 30 kg) is necessary in all close contacts.

All immunized contacts should also be given a booster dose of DPT/DT, if the last dose was received >2 years ago. Unimmunized contacts must be started on primary immunization schedule.

10.6 WHOOPING COUGH

Whooping cough (pertussis) is a highly contagious respiratory infection due to *Bordetella pertussis,* characterized by recurrent bouts of severe paroxysmal cough and typical *whoop* at the end of it. Incidence of pertussis has significantly declined in recent years due to widespread immunization.

Epidemiology: *B. Pertussis*-a gram negative coccobacilli, is present in nasopharyngeal secretions of clinical or subclinical infected case and spreads via droplets. *Infectivity period* spans from 1 week post-exposure to 3 weeks after onset of paroxysmal stage, with maximum infectivity in catarrhal phase.

W. cough is primarily a disease of infants and preschool children < 5 years, including newborns due to absence of maternal antibodies. Immunity after natural infection or immunization wanes after 3–5 years, responsible for increasing number of cases being seen in previously immunized older children and adolescents. Maximum cases occur in late winter/early spring season.

Pathogenesis: It is a *non-invasive* infection, with localized multiplication of organisms in respiratory epithelium with marked inflammation, necrosis and secondary infection. A specific *pertussis toxin* and other bioactive substances, produced by *B. pertussis,* contribute to pathology and development of immunity.

Clinical manifestations: Incubation period is 7–14 days. W. cough is a lengthy disease (also termed 100-day cough) with three stages:

- ***Catarrhal stage*** (2 weeks) begins as a non-specific upper respiratory infection with mild fever, coryza, conjunctival congestion and cough, which is initially dry, intermittent and irritating, mainly in nights.
- ***Paroxysmal stage*** (2–4 weeks), characterized by recurrent bouts of cough with typical sequence of events – each bout begins with sudden onset of

explosive cough, often precipitated by trivial stimuli, e.g. sucking, cold-exposure, etc. During the bout, the child is anxious, appears choked with suffused face and frequent protrusion of tongue. At the end of bout, the hallmark *whoop*—an inspiratory crowing sound, is produced by air rushing-in during inspiration, through partially closed glottis. Most episodes usually terminate with vomiting and production of small, thick-tenacious sputum. Child appears exhausted and sweats profusely.

Frequency and severity of paroxysm increase gradually over next few weeks, till convalescence.

- ***Convalescent stage*** (2–4 weeks) is associated with decreasing frequency and severity of cough bouts, return of appetite and general well-being.

Clinical examination may reveal complications of explosive cough, e.g. conjunctival hemorrhage or tongue lacerations, but no significant lung findings.

Complications may develop due to forceful coughing, secondary infections and reduced dietary intake, as child is scared of feed-precipitated bouts **(Table 10.11)**.

Diagnosis must be suspected in any unimmunized preschool child with prolonged cough (>14 days) and at least one of the following features: *(a) paroxysmal nature, (b) typical whoop* and/or *(c) post-tussive vomiting*. Absolute *lymphocytosis* is common and supports the diagnosis. Further confirmation is possible with:

- *Rapid diagnostic tests*, e.g. direct fluorescent antibody test in nasopharyngeal secretions or laryngeal swab. Serological tests, e.g. ELISA to detect major pertussis antibodies are sensitive, but not in early stages.
- *Culture* on *Bordet-Gengou media* either from naso-pharyngeal swab *or preferably* by direct inoculation (asking the baby to cough directly on culture-plate) is the *gold standard* for diagnosis, though yield is maximum in catarrhal stage.
- *PCR test* in nasopharyngeal secretions. Cultures or PCR tests are often negative in partly-immunized cases or in late paroxysmal stage.

D/D includes other causes of whoop or paroxysmal cough, e.g. (a) other infections, e.g. *B. parapertussis*, mycoplasma, chlamydia, adenoviral infections, (b) airway foreign body, (c) tubercular lymph nodes, compressing trachea/bronchi, etc.

TABLE 10.11: Complications of W. cough

- **Respiratory**
  Early : Pneumonia, atelectasis, pneumothorax
  Late : Bronchiectasis, reactivation of TB
  Others : Otitis media, subcutaneous emphysema
- **Neurological**
  Early : Hypoxic seizures, intracranial hemorrhage
  Late : Motor deficits, aphasia, blindness, deafness
- **Hemorrhagic**: Subconjunctival hemorrhage, epistaxis
- **Gastrointestinal**: Rectal prolapse, hernia
- **Malnutrition**, due to vomiting and ↓ intake

Treatment: Pertussis is self-limiting, with a limited role of antimicrobial therapy, unless instituted in very early stage. All infants < 6 months or older children with complications, must be hospitalized.

Management aims to limit the number of paroxysms, maintain the nutrition and general health, and treat complications, by:

- ***Isolation*** for at least 5 days after starting erythromycin therapy,
- ***Prevention of attacks*** by nursing in quiet comforting environment, avoidance of large feeds and exposure to cold draught,
- ***Management of acute attack*:** Though reassurance is usually enough to relieve anxiety, prolonged attack may need airway maintenance, oxygen or ventilatory support. Nebulized salbutamol may be effective in controlling the attack.
- ***Antibiotic therapy*** with Azithromycin (PO 10 mg/kg/day q24hr × 5 days) or other macrolides are effective only if given in early catarrhal stage. It shortens the natural course, reduces severity as well as infectivity and prevents secondary infection.

  Other agents, e.g. steroids, salbutamol, hyper-immune pertussis immunoglobulin, etc. are of no proven value.
- ***Supportive treatment*** to ensure adequate hydration, nutrition and treatment of complications.

Prevention depends on:

- ***Routine immunization*** with whole-cell killed vaccine (DTwP) or acellular pertussis vaccine (DTaP) at 6th, 10th and 14th weeks of life with booster at 18 months and 5 years (see Ch 9.2.1)
- ***Isolation of the index case***, specially from high-risk contacts, e.g. newborns.
- ***Prompt treatment of contacts:*** Since pertussis is highly contagious with secondary attack rate of 60–70%, all unimmunized household contacts <7 years of age should receive PO Azithromycin for 5 days or erythromycin for 14 days, along with immediate pertussis vaccination including those who received their 3rd primary dose before 6 months or booster dose before 3 years.

10.7 ENTERIC FEVER

Enteric fever, systemic infection due to Salmonella organisms, is a leading cause of prolonged pyrexia in children. While the term *enteric fever* includes both *typhoid* (*S. typhi*) and paratyphoid fever (*S. paratyphi* A, B and C), in practice it is used interchangeably with typhoid fever. Paratyphoid infections are less common, less severe and difficult to differentiate from typhoid.

Enteric fever is an endemic illness in India with occasional outbreaks and annual incidence of ~1% in population <17 years of age.

Epidemiology: *S. typhi* is a gram-negative, mainly intracellular organism, having 3 major antigens (O, H, Vi) and over 80 phage types. *Phage typing* is necessary to trace the source of epidemic.

Reservoir of infection is a case or carrier, who excretes the bacilli in urine or stools.

Modes of transmission is *fecooral,* due to contamination of food/water, either directly by hands of infected food handlers or indirectly via flies. Raw vegetables grown in sewage farms or washed with contaminated water are common sources of infection. Eggs with cracked shells may get contaminated during storage/transport. Transplacental and intrapartum infection due to fecal contamination of amniotic fluid in carrier mothers is known.

Risk factors: Enteric fever is more common in school-age and adolescents (5–19 years) and in males. It is rare during first two years of life due to less risk of exposure. Children with natural infection or immunization are *relatively* protected for 3 years. Peak incidence is during rainy season (July to September), due to higher risk of water contamination and fly population. Sewage-contaminated water supply, open air defecation and poor hygiene are other important risk factors.

Pathogenesis: On ingestion, Salmonella attach to microvilli of ileal brush borders and invade intestinal epithelium through Peyer's patches, to reach and proliferate in mesenteric lymph nodes (*local lymphoid hyperplasia*). From here, they enter blood stream via thoracic duct leading to asymptomatic *primary bacteremia* and seedling of reticuloendothelial tissues, e.g. liver, spleen, bone marrow, for further proliferation. After an incubation period of 7–14 days, *secondary bacteremia* develops from these sites, marking the onset of fever as well as infection of other tissues including gallbladder-*the most important reservoir of infection, responsible for carrier state.*

Pathology: Important pathological changes in enteric fever include:

- *Typical typhoid ulcers*-shallow oval ulcers along the axis of intestines, due to hyperplasia of Peyer's patches and slough of overlying epithelium,
- *Lymphoid hyperplasia* in mesenteric nodes, liver and spleen with mononuclear infiltration.
- *Metastatic micro-abscesses* in deeper tissues, due to secondary bacteremia.

Clinical manifestations: After incubation period of ~10–14 days, enteric fever presents with: (a) typical *remittent fever with step-ladder pattern* (gradual rise in first week), though many cases have continuous fever, (b) constitutional symptoms, e.g. malaise, anorexia, myalgia, headache, and (c) GIT symptoms, e.g. abdominal pain, constipation or diarrhea. Important clinical signs include:

- Ill or toxic general appearance,
- Relative bradycardia,
- Dry and coated tongue,
- Tympanic abdomen with mild to moderate hepato-splenomegaly, and
- Typhoid rash (*rose spots*)—discrete macular blanching lesions over trunk on 7^{th}–10^{th} day, rarely visible in dark-skinned Indians.

Clinical manifestations are usually mild in younger children (<5 year) and paratyphoid fever.

Complications: Although fever and physical findings may resolve spontaneously in 2–4 weeks, complications are common in untreated cases, usually during 2nd–3^{rd} weeks of illness **(Table 10.12)**. Mortality is <1% in treated cases.

Diagnosis should be considered in any case with: (a) prolonged fever without localizing signs, and (b) toxic appearance with coated tongue and tympanic abdomen. Confirmation requires:

- *Bacterial cultures:* Blood cultures are positive in 60–80% cases during first week, but positivity declines in later weeks. Multiple cultures, with volume not less than 5 ml on different days, are preferable as typhoid bacteremia is low-grade and intermittent. Bone marrow culture is more sensitive (85–90% positivity), even after antimicrobial therapy. Stool and urine cultures turn positive by 3^{rd}–4^{th} weeks and help in diagnosis of carrier state.
- *Serological tests:* Classical *Widal test* measures titers of agglutinin antibodies against O and H antigens and turns positive only after 5–7 days of fever. Generally, anti-O titers of >1:160 *or* rising anti-H titers on second test after a week, are considered as suggestive (but not diagnostic) of enteric fever. Single anti-H titers may be false-positive due to *anamnestic response* to other fevers, e.g. malaria and rickettsial infections. Anti-O titers do not differentiate between typhoid and paratyphoid infection.

  Rapid serodiagnosis tests, e.g. *Typhidot* to measure IgM antibodies against outer membrane protein of

TABLE 10.12: Complications of enteric fever

- **Gastrointestinal:**
  - Intestinal bleeding (1–10%)
  - Perforation, peritonitis
- **Hepatobiliary:** Hepatitis, cholecystitis
- **Respiratory:** Pneumonia, bronchitis
- **Neurological:**
  - Encephalitis, meningitis, psychosis
  - Acute cerebellar ataxia,
  - Peripheral neuritis, Guillain-Barré syndrome (rare)
- **Skeletal:** Osteomyelitis, arthritis
- **Deep tissue abscesses** in liver, spleen, etc.
- **Blood:** Aplastic anemia, thrombocytopenia
- **Miscellaneous:**
  - Parotitis
  - *Rare:* Myocarditis, acute nephritis

organism using ELISA technique have a sensitivity and specificity of ~80%.

- Direct detection of *S. typhi* specific antigens in serum using *monoclonal antibodies* is possible but not routinely available.
- *PCR testing* is expensive but most specific and sensitive diagnostic method for early diagnosis, even in cases with very low bacteremia.
- *Other investigations* are largely supportive, to detect complications or exclude other causes of prolonged pyrexia and include: (a) *hemogram* (leucopenia with relative lymphocytosis), (b) *platelet counts* (thrombocytopenia), (c) stool examination for occult blood to exclude GIT bleeding, (d) *chest X-ray* to exclude pneumonia or tuberculosis (e) *standing X-ray abdomen* to exclude perforation, and (f) *USG abdomen* to exclude peritonitis, cholecystitis and metastatic abscesses in children with prolonged illness.

Management aims to: (a) eradicate infection as well as carrier state, (b) provide nutritional support and symptomatic relief, and (c) diagnose and treat complications promptly.

Hospitalization is indicated in cases with acute toxemia, poor intake or suspected complications. Important treatment modalities include:

- ***Antimicrobial therapy*:** Conventional antibiotics, e.g. chloramphenicol, ampicillin or cotrimoxazole are rarely used at present due to widespread resistance. Quinolones are the drugs of choice for treatment of enteric fever in adults, but not uniformly approved in children. Current IAP recommendation (2022) are as follows:
  - For *uncomplicated enteric fever*, PO Cefixime (20 mg/kg/day q12hr 7–14 days) is the preferred choice, the alternative being PO Azithromycin (20 mg/kg/day q24hr 7–14 days).
  - For *complicated or severe disease*, IV Ceftriaxone (100 mg/kg/day q12hr) or Cefotaxime (150–200 mg/kg/day q12hr) is the preferred choice, to be given for 10–14 days. Alternatives include IV Aztreonam (50–100 mg/kg/day q12hr) or Azithromycin (20 mg/kg/day q12hr) for 7 days, in cases of penicillin allergy or poor response.
- ***Supportive treatment*** includes: (i) bed rest, (ii) soft diet, (iii) fluid and electrolyte therapy, and (iv) general nursing care, especially for oral hygiene. *Steroids* (PO/IV for 2–3 days) may be used in cases with severe toxemia, shock or mental obtundation, though prolonged steroid therapy increases the risk of intestinal perforation.
- ***Treatment of relapse:*** Relapses are common after partial treatment, usually within two weeks of stopping antibiotics. Each relapse should be treated as a fresh case, but for longer duration.
- ***Eradication of carrier state:*** Persistent excretion of Salmonella in stool/urine after defervescence defines a '*carrier state*', which includes convalescent carriers (<3 months) and chronic carriers (>3 months). Carrier state is less common in children (1–5%) than adults.

Reservoir of infection in carriers is *gallbladder* and treatment includes: (a) *medical therapy* with PO ampicillin or amoxicillin for 2–4 weeks till at least two stool cultures are negative, and (b) *surgery*, i.e. cholecystectomy in chronic carriers (>1 year) refractory to repeated antibiotics therapy for 4–6 weeks, to remove the reservoir of infection

Prevention against enteric fever includes—(a) general sanitation and supply of safe drinking water, (b) personal and food hygiene awareness, (c) immunization, and (d) detection, treatment and follow-up of carriers. Stool/urine cultures are indicated in all cases after 3–4 months of recovery to exclude carrier state.

Currently, two types of typhoid vaccines are available: (a) Vi polysaccharide vaccine and (b) conjugate vaccine. Polysaccharide vaccines are less effective, cannot be used < 2 years and need boosters every 3 years.

While Typhoid vaccination is not included in universal immunization program, IAP recommends a single dose of typhoid conjugate vaccine (TCV) at the age 6–9 months, with catch-up immunization upto 18 years (Ch 9.2.2).

Non-typhoidal salmonellosis due to other *Salmonella* species, e.g. *S. enteritidis, S. choleraesuis, S. typhimurium, S. newport*, etc., is usually acquired by use of contaminated animal products, e.g. eggs *or* raw vegetables/water.

Clinically these cases present as: (a) *acute gastroenteritis* (food poisoning) with crampy abdominal pain after ~ 24 hours of consumption, *or* (b) *extraintestinal disease*, e.g. osteomyelitis, arthritis or meningitis, which is more common in newborns, severe malnutrition, sickle cell anemia, malignancy and immunodeficiency states.

Diagnosis rests on culture and phage typing, though serological tests, e.g. latex agglutination test or immunofluorescence test are available for early diagnosis.

Treatment of Salmonella gastroenteritis is symptomatic, *without antibiotics*, which may prolong carrier state. Extraintestinal disease should be treated like enteric fever, but more intensively, via parenteral route only.

10.8 SHIGELLOSIS

Shigellosis is the commonest cause of bacillary dysentery in children, characterized by: (a) typical small volume, bloody-mucoid stools with extreme frequency, (b) high fever with toxic appearance and (c) risk of systemic complications.

TABLE 10.13: Complications of Shigellosis

- Dehydration, dyselectrolytemia
- Hypoglycemia
- Septicemia and DIC
- Seizures, encephalopathy*
- Renal failure, hemolytic uremic syndrome
- Hemolytic anemia, thrombocytopenia
- *Local:* Rectal prolapse, toxic megacolon
- *Others***:* Arthritis, Reiter syndrome, hepatitis, myocarditis

**Ekeri syndrome*: Hyperpyrexia, toxic appearance, seizures, coma and death, without significant sepsis/dehydration
***? autoimmune ?? toxin-mediated

Epidemiology: Shigellosis is caused by one of the four species—*S. dysenteriae* (commonest), *S. flexneri, S. boydii* and *S. sonnei*. Contaminated food and water is the commonest source of infection, though person-to-person transmission through infected food handlers is common.

High-risk factors: It is most common in pre-school age group (except in breastfed infants due to protective antibodies in breast milk) and institutionalized children, e.g. orphanages and daycare centers. While most cases are endemic in India, intermittent outbreaks are common in rainy season.

Pathogenesis: Shigella requires very low inoculum to produce clinical disease, mainly caused by invasion of colonic epithelium (invasive disease). However, some strains of *S. dysenteriae* produce a powerful exotoxin—*Shiga toxin* and/or an endotoxin *(ShET1).*

Pathological lesions are characterized by intense mucosal inflammation and formation of multiple ulcers, mainly in *distal colon*. Development of secretory IgA and type-specific serum antibodies leads to spontaneous recovery after 7–10 days in uncomplicated cases. Chronic diarrhea is rare.

Clinical manifestations develop after a short incubation period of 1–3 days, with:

- Acute watery diarrhea, which rapidly evolves into typical small-volume blood and mucus mixed stools with high frequency (15–20/day), urgency, painful defecation (strangury) and colicky abdominal pain.
- High fever, toxic appearance and other constitutional symptoms.
- Extraintestinal manifestations and complications in ~ 30–40% cases **(Table 10.13)**.

Diagnosis is supported by presence of leukocytes (usually >50–100/hpf) and blood in stools and peripheral leukocytosis with band cells. Confirmation requires stool culture (or rectal-swab cultures) on selective media, e.g. xylose-lysine deoxycholate (XLD) and Salmonella-Shigella agar. However, negative culture does not exclude shigellosis. Molecular PCR tests are available but rarely used.

TABLE 10.14: Common causes of dysentery

- *Bacterial:*
  - Shigella
  - *E. coli* (enteroinvasive serotypes)
  - *C.difficile* (pseudomembranous enterocolitis)
  - *Others: C. jejuni, Y. enterocolitica*, Salmonella
- *Protozoal: E. histolytica*
- *CIBDs:* Ulcerative colitis, Crohn's disease

CIBD: Chronic inflammatory bowel diseases

D/D of shigellosis includes other causes of infective dysentery and acute attack of chronic inflammatory bowel diseases, e.g. ulcerative colitis **(Table 10.14)**.

Management includes: (a) fluid and electrolyte correction, (b) antibiotic therapy, and (c) symptomatic measures.

Antibiotics of choice for shigellosis are Ciprofloxacin (PO 20–30 mg/kg/day q12hr) or Cefixime (PO 8 mg/kg/day q12hr) for 5 days, while IV Ceftriaxone (50 mg/kg/day OD) may be used in small infants or seriously sick patients. Azithromycin is a second-line antibiotic in non-responders.

Studies have also shown beneficial effects of single dose vitamin A (200000 IU) and zinc supplements (PO 20 mg 14 days) in recovery from shigellosis, apart from high-protein, high-caloric diet.

Most cases recover within 5–7 days and mortality is uncommon except in severe malnourished children or those with complications, e.g. severe dyselectrolytemia, DIC, renal failure and encephalopathy.

Prevention depends on: (a) prolonged breastfeeding, (b) personal hygiene, e.g. hand-washing after defecation/before food handling and (c) proper water/sewage treatment. No vaccine is available at present.

IMNCI recommends diagnosis of *dysentery* in any child age 2 months-5 years with blood in stools, who should be treated with Cefixime (PO 10 mg/kg/day q12hr) for 5 days and Tab Zinc 20 mg once a day (half tab in infants 2–6 months), with follow-up after 2 days.

10.9 *H. INFLUENZAE* B DISEASE

Haemophilus influenzae b *(Hib)* infections are commonest cause of meningitis and pneumonia in young children (6 months–3 years) of developing countries, though the incidence seems to be substantially reduced due to widespread immunization.

Epidemiology: *H. influenzae*, a gram-negative coccobacilli, exists in capsulated or uncapsulated forms, with 6 serotypes (a–f). Invasive disease is caused by *capsulated serotype b*, while other serotypes or uncapsulated organisms may cause localized airway disease or invasive disease in immunocompromised host.

High-risk factors: There is a striking age distribution of invasive Hib disease, with >90% cases seen within first 5 years of life. In older children, it is more likely in immunocompromised children specially with *splenic dysfunction*, e.g. sickle cell disease, asplenia and splenectomy.

Pathogenesis: Hib organisms colonize respiratory flora via droplet infections-colonization rate being directly related to age. As colonized individuals develop natural immunity in due course of time, uncolonized infants and young infants are more susceptible for Hib disease at the time of first infection. Infection may spread locally *or* via hematogenous route to distant sites (invasive disease).

Clinical spectrum of Hib disease varies from *localized disease*, e.g. otitis or sinusitis to *invasive disease,* i.e. meningitis, pneumonia or septicemia **(Table 10.15)**.

Diagnosis depends on the culture and serotyping of organism, which requires prompt transport and inoculation as the organism is very fastidious.

A latex agglutination test to detect antibodies against capsular polysaccharide antigen, i.e. polysaccharide reactive proteins (PRP) in CSF or other secretions is very useful for early diagnosis, especially in partially-treated cases.

Treatment depends on the severity of disease. While PO Amoxycillin or Co-amoxclav for 7–10 days is usually adequate for localized disease, intensive parenteral therapy with a third-generation cephalosporin, i.e. *Ceftriaxone* is essential in invasive disease.

Prevention of Hib disease involves:

- ***Routine Hib immunization*** with a conjugated polysaccharide vaccine, given at 6,10 and 14 weeks as a combination pentavalent vaccine in NIS, without any booster dose. However, IAP recommends three primary doses as in NIS, along with a booster dose at 12–18 months. Catch-immunization is not recommended beyond 5 years of age, except in *high-risk cases*. (Ch 9.2.1)
- ***Post-exposure chemoprophylaxis*** with *Rifampicin* (10–20 mg/kg OD for 4 days) is indicated in close contacts of confirmed cases, who are unimmunized and <5 years of age.

TABLE 10.15: Clinical spectrum of Hib disease

Localized disease:
- Otitis media
- Sinusitis
- Acute epiglottis
- *Others:* Orbital cellulitis, conjunctivitis

Invasive disease:
- Meningitis
- Pneumonia
- Bacteremia
- *Others:* Arthritis, pericarditis, peritonitis

10.10 MENINGOCOCCAL INFECTIONS

Meningococcal infections usually occur in small outbreaks, presenting as *localized* meningococcal meningitis or *systemic* meningococcemia.

Epidemiology: According to antigenic differences in capsular polysaccharide, *Neisseria meningitides* are divided into 13 serotypes. Of these, six (A, B, C, W, X and Y) account for virtually all cases of meningococcal disease. Group A infections are more common in India.

High-risk factors: Meningococcal disease is more common in young infants (3–24 months). Newborn <3 months are protected by transplacental maternal antibodies. Older children are also relatively protected by antibodies acquired during previous colonization, though those with complement-deficiency states, e.g. nephrotic syndrome, hepatic failure and autoimmune disorders, are more susceptible for these infections.

Pathogenesis: Meningococcal infection is a highly contagious droplet infection with nasopharyngeal colonization rate as high as ~100% during outbreaks. Post-colonization, infection may remain asymptomatic (colonization) or disseminate hematogenously (invasive disease), to produce meningococcemia and secondary involvement of meninges, skin, adrenals and other organs.

Pathologically, invasive disease is characterized by acute inflammatory reaction (meningitis), vasculitis (rash) and tissue hemorrhages, especially in adrenals (*Waterhouse-Friderichsen syndrome*), due to a DIC-like state.

Clinical spectrum of disease varies from mild fever and occult bacteremia to a shock-like state and death. Common presentations include:

- ***Acute meningococcemia***, begins as a flu-like illness with fever, sore-throat, headache, myalgia and pathognomonic *purpuric skin rash*, but may progress rapidly to septic shock, hypotension, DIC, adrenal hemorrhage (*Waterhouse-Friderichsen syndrome*) and multi-organ failure. Meningitis may or may not be present.
- ***Acute meningitis*** is most common manifestation, with/without skin lesions or signs of meningococcemia.
- ***Non-CNS focal disease***, e.g. pericarditis, pneumonia or arthritis is rare.
- ***Chronic meningococcemia*** is rare, with prolonged intermittent fever and rash, arthralgia and headache during fever, lasting for 6–8 weeks.

Complications of meningococcemia include: (a) metastatic infections, e.g. pneumonia or arthritis (b) adrenal hemorrhage, (c) cutaneous vasculitis, leading to skin gangrene and (d) late complications, e.g. immune complex arthritis or cutaneous vasculitis, after 6–9 months.

Diagnosis rests on isolation of organism from blood, CSF or skin lesion. A positive throat culture is not diagnostic and may reflect only the carrier state. Early diagnostic tests, e.g. latex agglutination test, are useful but not as replacement of the culture. Molecular PCR tests are available with high sensitivity and specificity.

Treatment: IV Ceftriaxone 100 mg/kg/day q12–24 hr for 5–7 days is preferred at present over conventional high-dose Penicillin therapy (2–3 Lac U/kg/d q4–6 hr) due to dosage convenience and eradication of nasopharyngeal carrier state. Allergic cases may be treated with ciprofloxacin or meropenem.

Prevention includes:

- ***Post-exposure chemoprophylaxis:*** All close-contacts should receive Rifampicin (PO 10 mg/kg BD for 2 days) or a single dose of ciprofloxacin or ceftriaxone. Since penicillin does not eradicate nasopharyngeal carriage, even index case should receive chemoprophylaxis, if treated by penicillin and not ceftriaxone before discharge.
- ***Pre-exposure immunization*** with a quadrivalent conjugate vaccine (MCV) is recommended only in high-risk cases or during outbreaks as follows: (a) high-risk cases with two doses at 8 weeks interval, followed by a booster dose every 5 years, (b) during outbreaks, a single dose to close-contacts above 3 months of age, (c) single dose to laboratory or health care workers at risk of exposure with booster every 5 years, if required, (d) for international travels (Ch 9.2.2)

  Polysaccharide vaccines (MPSV) are also available but should be used only in high-risk children >2 years if MCV is not available, given as a single dose followed by revaccination every 3–5 years. During outbreaks too, a single dose of PPSV may be given in children > 2 years or two doses at 3 months interval in younger children 3–24 months of age (Ch 9.2.2).

10.11 CHOLERA

Cholera is an ancient killer disease, with many pandemics recorded in different parts of the world with very high mortality. In India. Disease is currently endemic throughout the country, with intermittent focal outbreaks.

Epidemiology: Cholera is caused by different strains of *vibrio cholerae 01*, a gram-negative motile, slightly curved rods with polar flagellum.

V. cholerae 01 has two major biotypes—*classical and El Tor vibrio*, subdivided into many serotypes (serovars) according to somatic antigens—mainly the *ogawa*, *inaba* and *hikojima* strains.

Current infections in India are mainly caused by El Tor biotype and ogawa serotypes. Last two decades have seen emergence of a new virulent strain *V. cholerae 0139* from Chennai, responsible for the many outbreaks in India and south Asia.

Source of infection is an asymptomatic carrier or a case, and infection is transmitted *feco-orally* after ingestion of contaminated water or food. *Period of infectivity* is 7–10 days for a case, though chronic carrier state may continue for >10 years.

Cholera affects all age groups with highest attack rate and more severe disease in children. Most outbreaks begin in summer or rainy season, with two important risk factors—poor sanitary conditions and large congregations of people, e.g. in fairs, *kumbhs*, etc.

Etiopathogenesis: *V. Cholera, o*n reaching the small intestine, proliferate and colonize the duodenum/jejunum to produce various enterotoxins. Two important enterotoxins include:

a. A cholera toxin, which activates adenylate cyclase to raise cyclic AMP levels in intestinal mucosa, with decreased sodium and chloride absorption as well as increased chloride secretion.
b. A *zonula occludens* toxin *(zot),* which alters the intercellular tight junctions to increase intestinal mucosal permeability and leakage of water and electrolytes into lumen.

Clinical manifestations depend on the type of strain, dose of organisms and age of the patient. El Tor infections are frequently asymptomatic (>95%) as compared to classical Vibrio (<20%).

A typical case present after an incubation period of 6 hours – 5 days, with 3 stages:

a. *Stage of evacuation* characterized by abrupt onset of profuse, painless, watery diarrhea *(rice-water stools)* with fishy odor and vomiting.
b. *Stage of collapse* due to extensive fluid and electrolyte loss with severe dehydration, shock, hypothermia, renal failure and acidosis. Patient develops intense thirst and muscular cramps due to dyselectrolytemia, and gradually becomes disoriented or stuporus. Purging can continue for as long as one week, unless untreated patients die due to dehydration and acidosis.
c. *Stage of recovery* in survivors begins with decreased frequency, better consistency, appearance of color (bile) in stools and improved hydration.

However, classical presentation is seen in only 10–15% cases while other children present with milder non-specific diarrhea and recover within 1–3 days.

Diagnosis should be suspected in any case from endemic region, presenting with profuse diarrhea and/or rice-water stools. Confirmation requires:

- *Direct stool microscopy (hanging-drop preparation)* under dark-field illumination for motile Vibrio, which appear like many *shooting stars in the dark sky*. Motility ceases on mixing with polyvalent anti-Vibrio

sera. Stools should be collected before antimicrobial therapy on a transport media, e.g. *Venkatraman-Ramakrishnan media* or alkaline-peptone water and transported to the laboratory immediately for direct motility examination and culture.

- *Stool cultures* are necessary for confirmation, bio-typing, sero-typing and phage-typing of infections for epidemiological purpose. Cultures are done on bile-salt agar media, e.g. *thiosulfate citrate bile sucrose* (TCBS), after initial enrichment in peptone-water tellurite media.
- *Serological tests* are not useful except for epidemiological studies and molecular identification with PCR-DNA probes is possible but rarely used.

Management: Prompt management is essential to reduce mortality, prevent further transmission and control the outbreak and includes:

- ***Fluid and electrolyte therapy:*** Over 90% cases of cholera can be managed with ORS alone, which should be started as early as possible and given *ad libitum* with minimum 75 ml/kg during first 24 hours *plus* 50–100 ml after each stool. IV fluid therapy with Ringer lactate is required in cases with: (a) severe dehydration and shock, (b) persistent vomiting, and (c) altered sensorium (*see* Ch 7.7 for fluid therapy).
- ***Antimicrobial therapy:*** Antibiotics shorten the course of illness and reduce the risk of transmission. Drugs of choice, in order of preference, are PO *Tetracycline* 50 mg/kg/day q6hr or PO *Erythromycin* 50 mg/kg/day q6hr, both for 3 days. Single dose PO *Ciprofloxacin* 20 mg/kg or *Azithromycin* 20 mg/kg are equally effective.
- ***Continuous monitoring*** for intake/output of fluids, hydration status and electrolyte disturbances.
- ***Adequate parenteral nutrition*** in critically sick children, though oral feeds should be started as soon as possible.
- ***Treatment of complications***, e.g. (a) circulatory shock, (b) electrolyte disturbances, e.g. *hypokalemia* due to excessive stool loss or *hypocalcemic tetany* due to persistent vomiting, (c) acidosis, (d) hypoglycemia, (e) neurological depression due to hypovolemia and hypoxia, and (f) pulmonary edema due to fluid overload.

Prevention: Control of cholera outbreak is a major public health exercise, involving:

- *Immediate notification* to the authorities,
- *Early detection* of cases and asymptomatic carriers by contact-stool examinations and door-to-door survey in affected locality,
- *Public health measures* to improve sanitary conditions and excreta disposal,
- *Proper disposal/disinfection* of infectious biomedical waste,
- *Vaccination is* recommended only in special circumstances, e.g. residents and travellers of highly endemic regions and high-risk settings for outbreaks, e.g. *kumbh*. It should not be used as outbreak control measure.

  Two types of whole-cell killed oral cholera vaccines are available, of which only a bivalent vaccine (Shanchol) containing *V. cholerae* 01 (classic and El Tor) and *V. cholerae* 0139 serotypes is licensed in India, to be given orally as two doses at two weeks interval, only beyond two years of age.

10.12 BRUCELLOSIS

Brucellosis, caused by *B. melitensis* in India is a zoonotic disease of cattle, with humans infected by ingestion of contaminated animal products, e.g. unpasturized milk. It is a major public health problem in adults specially cattle-handlers, but rare in children.

Clinical manifestations begin after 3–4 weeks of incubation period, with a triad of: (a) prolonged fever, (b) arthralgia, and (c) hepatosplenomegaly. Constitutional features, e.g. GIT upset, sore throat, headache/lethargy and rash may be present. Invasive brucellosis, e.g. osteomyelitis, meningitis or endocarditis is extremely rare in children.

Diagnosis rests on clinical suspicion in prolonged pyrexia with *rising serological titers*, i.e. serum agglutination test on acute and convalescent sera. It is confirmed by culture or PCR.

Treatment: Doxycycline (PO 2–4 mg/kg/day q24hr) with Streptomycin (IM 15–30 mg/kg/day q24hr) or Rifampicin (PO 15–20 mg/kg/day q24hr) is the drug of choice for older children, while younger ones may be treated by cotrimoxazole with rifampicin, for 6 weeks. Invasive brucellosis requires at least 4–6 months therapy with three drugs-doxycycline, streptomycin and rifampicin.

10.13 CHILDHOOD TUBERCULOSIS

Tuberculosis (TB) continues to be major public health problem in India and recent years have witnessed resurgence of disease due to spread of HIV infection and emergence of multi-drug resistance. However, India is committed to eliminate tuberculosis by the year 2025, ahead of WHO-target for global TB elimination by 2030.

Magnitude of problem: Natural course of tuberculosis may be divided into two stages:

a. Primary infection that may or may not progress to disease state and
b. Active disease, due to spread of primary infection, re-activation of latent primary infection *or* re-infection in later life.

Accordingly, the magnitude of problem is ascertained by the frequency of either *infection* or *disease.* Recent TB report 2023 suggests estimated prevalence of disease in India as 312 per lakh population, including 5.6% children below 14 years of age. However, ~30–40% children by this age are Tuberculin-positive, suggesting a large pool of latent infections. Year 2022 has reported ~13% rise in newly detected cases *vs* previous year, perhaps due to delayed medical attention in COVID years and increase in the case detection/notification under National Tuberculosis Elimination Programme (NTEP).

Epidemiology: *Mycobacterium tuberculosis*—an obligate aerobe, is characterized by hallmark *acid-fastness,* i.e. capability to resist decolorization by acid or alcohol on staining. Presence of a lipid-rich cell wall resists intracellular killing and hence, the organism may survive for many years intracellularly within phagocytes and macrophages, even after extracellular destruction.

Genus *Mycobacterium* includes two broad groups—(a) *Typical mycobacteria*, e.g. *M. tuberculosis, M. bovis,* etc. and (b) *Atypical mycobacteria*. While atypical mycobacteria can also produce similar disease specially in immunocompromised hosts, the term *tuberculosis* is reserved for disease caused by typical mycobacteria, of which *M. bovis* is rare in India.

Atypical mycobacteria are classified as: (i) photochromogens, e.g. *M. kansasii*, (ii) scotochromogens, e.g. *M. scrofulaceum*, (iii) nonphotochromogens, e.g. *M. intracellulare*, and (iv) rapid growers, e.g. *M. fortuitum*.

Primary infection is most common in early childhood with important risk factors being malnutrition, low socioeconomic status and absence of BCG vaccination.

Overcrowding and history of contact in the household are two most important environmental factors for natural infection.

Source of infection is usually an adult sputum-positive household contact. While effective therapy reduces the infectivity of index case by 90% within 48 hours, intermittent discharge of organisms in sputum may continue for 3 months (or longer in drug-resistant cases). Pediatric cases are seldom infective, unless having endobronchial or cavitatory lesions.

Mode of transmission is usually a *direct* person-to person droplet infection, or rarely via *indirect* contact with contaminated fomites. Newborns of infected mother may be infected via transplacental infection or after aspiration of infected amniotic fluid at birth.

Portal of entry: Lung is the commonest portal of entry in acquired infections, including in newborns due to aspiration of amniotic fluid at birth. However, congenital transplacental infection may be first lodged in liver.

Pathogenesis (Natural history) of infection depends on previous exposure and presence of cell-mediated immunity (CMI). In most cases of childhood infections, when infection is often primary and CMI is absent, infection progresses in following manner:

- ***Formation of primary complex:*** After airborne entry, bacilli are primarily lodged in *peripheral subpleural alveoli around the right interlobar fissure* (due to sluggish air current in this region) and multiply in alveolar spaces and ducts. About 20% cases have more than one primary lesion. In transplacentally infected infants, primary lesion forms in liver with similar course.

  First protective response to infection is nonspecific local inflammatory reaction to attract macrophages, which attempt to ingest and destroy invading pathogens. However, presence of unique sulfatides molecules in mycobacterial cell wall inhibits phagocytic activity and many organisms escape intracellular destruction and in fact, multiply intracellularly.

  During this period of uninhibited growth, bacilli either remain concentrated in parenchymal lesion (*Ghon lesion*-a pulmonary granuloma of ~1 cm size with central necrosis and surrounding mononuclear infiltration, epitheloid cells and giant cell formation) *or* carried to regional lymph nodes via local lymphatics. The term *primary complex* includes: (i) parenchymal (Ghon) lesion, (ii) draining lymphatics, and (iii) regional lymph node infection.

  Till adequate and specific immune response develops in next 8–12 weeks (as discussed below), local lesion progresses relentlessly with intense tissue reaction. During this period, intermittent bacteremia is common with hematogenous seedling of distant organs (*extrapulmonary tuberculosis*).
- ***Immunological response:*** Four different types of specific immunological responses develop in next 8–12 weeks, which determine the further course of disease:
  - *Specific macrophage-mediated response:* After initial non-specific macrophage response, small population of lymphocytes with capability to recognize specific mycobacterial antigens proliferate and secrete lymphokines and other inflammatory mediators, to enhance the bactericidal activity of activated macrophages and trigger humoral/cellular response.
  - *Humoral response:* Although tubercular infection provokes a robust antibody response, humoral immunity plays negligible role to protect from progression of disease.
  - *Cell-mediated immunity* (CMI), i.e. T-cell mediated immune response is the most important protective response to arrest primary lesion. Development of adequate CMI leads to healing of primary complex, while inadequate CMI permits unhindered progression. Persistence of adequate CMI is essential to keep healed lesions in check, as intracellular pathogen often survive in these lesions and may

be reactivated during immunocompromised states, e.g. malnutrition, diseases, e.g. measles, whooping cough, HIV, etc. and steroid or cytotoxic therapy.
  - *Delayed tuberculin hypersensitivity* (DTH) is a potentially harmful response that arrests the mycobacterial growth but provokes intense tissue reaction and destruction due to release of bacterial breakdown products and inflammatory mediators like TNF- , hydrolytic or proteolytic enzymes, oxidation intermediates, etc. DTH is also responsible for tuberculin positivity and other hypersensitivity manifestations **(Table 10.16)**.
- ***Fate of primary complex*** after initial 6–10 weeks **(Table 10.17)**, depends on the balance between protective CMI and destructive DTH in the host:
  - In >90% cases, development of adequately CMI heals primary lesion with calcification.
  - In cases with inadequate CMI, (e.g. in malnutrition), healing is incomplete with progression of disease (*see* below, *spread of primary lesion)*. Even in partially healed lesions, viable organisms may persist for many years.
  - In cases with excess DTH (with/without adequate CMI), local reaction is so intense as to cause excessive tissue destruction and cavity formation. Uncommon in primary infection, it is the major pathological mechanism of *adult or reactivation TB*.
  - ***Spread of primary lesion:*** In children with poor CMI and/or high DTH, primary lesion may progress locally (*progressive primary complex*), invade neighbouring bronchi (*endobronchial disease*) or vessels (miliary disease) **(Fig. 10.2)**. Regional mediastinal/hilar nodes may also enlarge to compress the bronchi or rupture into them.
    - *Progressive primary complex* is the least severe form of disease, characterized by slowly progressive concentric lesion (coin lesion) or segmental bronchopneumonia.
    - *Endobronchial rupture* of parenchymal or nodal lesion leads to the discharge of infective material into bronchial lumen, with following consequences: (a) diffuse spread to lung, i.e. *bronchopneumonia*, or (b) complete block of bronchus, i.e. *collapse* of distal lung, or (c) partial block of bronchus to act as a ball-valve mechanism, i.e. *emphysema* in distal lung.
    - *Hematogenous spread* may occur during early bacteremia at the time of primary infection or late bacteremia, due to invasion of vessels traversing infected lung tissue. Further course depend on the number of organisms leaked into blood stream. Sudden and heavy bacteremia may produce more serious *miliary tuberculosis*, while intermittent mild bacteremia may be silent or present later with *disseminated or extrapulmonary tuberculosis*.

      Invasion of extrapulmonary organs leads to formation of *satellite tubercular lesions* (granulomas) in different tissues, sometimes termed as *Rich's focus* in brain, *Simond's focus* in spleen and liver, *Sheehan's focus* in adrenals, etc. Most of these lesions remain silent for long time or progress slowly over 3–5 years to manifest as extrapulmonary TB.
    - *Lymphatic spread* via continuous channels from mediastinal nodes to cervical or abdominal nodes as well as direct spread of pulmonary/pleural lesion to ribs or spine, are other important modes of spread for tubercular disease.
- ***Re-activation/Re-infection tuberculosis*** is primarily seen in adolescents/adults and follows a different course than primary infection **(Table 10.18)**. Local response in these cases is modified by presence of prior DTH, leading to intense tissue reaction with cavitation. Reactivation/reinfection pulmonary lesions often develop in apical (*Puhl's lesion*) or infraclavicular region (*Assman's focus*).

TABLE 10.16: Hypersensitivity manifestations in TB

- Tuberculin positivity
- Phylectenular conjunctivitis
- Erythema nodosum
- Aseptic (Lincoln's) meningitis
- Pleural effusion

TABLE 10.17: Possible fates of primary infection

- **Complete healing with/without calcification**
- **Local progression**
  - Progressive primary complex
  - Segmental/lobar pneumonia
  - Pleural effusion
- **Endobronchial spread**
  - Consolidation
  - Collapse
  - Emphysema or pneumothorax
- **Hematogenous spread**
  - Acute miliary TB
  - Protracted disseminated TB
  - Localized extra-pulmonary TB
- **Lymphatic spread**
  - Cervical lymphadenopathy
  - Abdominal lymphadenopathy
- **Reactivation in later life**
  - Fibrocaseous tuberculosis (adult type)

Clinical spectrum of tuberculosis is extremely wide, depending on the type and extent of lesion and includes:

Primary complex is basically a radiological diagnosis and most cases are asymptomatic except mild constitutional symptoms, e.g. low-grade fever and anorexia. Mild dry

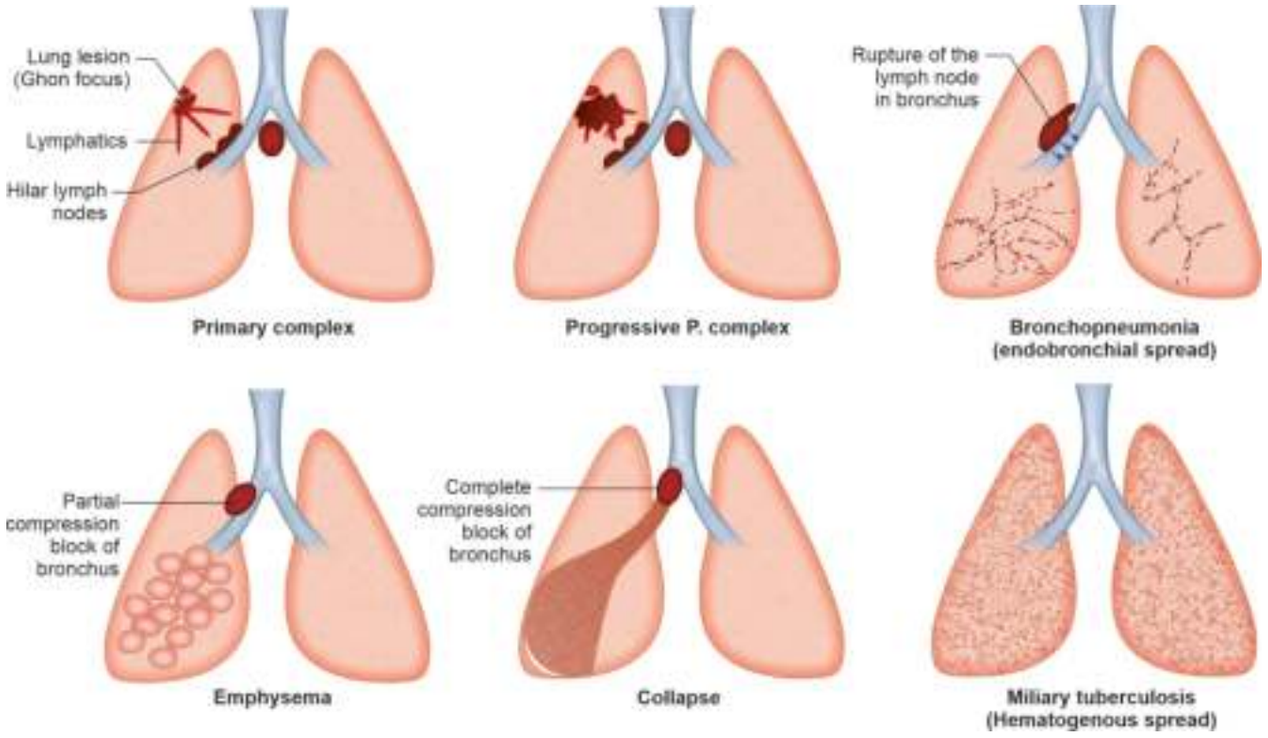

Fig. 10.2: **Various types of pulmonary tubercular lesions in children.**

TABLE 10.18: Primary vs Reactivation TB

Differences	***Primary***	***Reactivation****
Common age	<5 years	>7–8 years
Source of infection	Exogenous	Endogenous
CMI	Absent	Usually low
DHT	Absent	Present
Lung focus	Sub-pleural	Apical
Mode of healing	Calcification	Fibrosis
Mediastinal nodes	Enlarged	Minimal
Bacillary load	Low	High
Infectivity	Rare	Common
Hematogenic spread	Common	Rare

**or* re-infection

cough may be present due to compression of airways by enlarged mediastinal nodes.

Pulmonary tuberculosis, other than primary complex, presents with:

- Constitutional symptoms, e.g. mild evening-rise fever, anorexia, weight loss, night sweats, etc.
- Respiratory symptoms, e.g. dry/wet cough, respiratory distress, wheezing or stridor. Chest pain indicates pleural involvement.
- Signs of local disease, depending on the type of lesion.

In NTEP, *pulmonary tuberculosis (PTB)* refers to:

- Any confirmed or clinically diagnosed case of TB involving lung parenchyma or tracheobronchial tree, including intrathoracic lymphadenopathy (mediastinal or hilar), without radiological abnormalities in the lung.
- *Miliary TB* (discussed later) is classified as PTB due to lesions in the lungs.
- *PTB with extrapulmonary disease* (discussed later) is also classified as PTB.
- *Extensive pulmonary tuberculosis* refers to severe pulmonary bilateral cavitatory disease or extensive parenchymal damage on chest X-ray.

Miliary tuberculosis is the most serious manifestation (mortality >50%), usually presenting within first year of primary infection with acute onset of:

- High fever with severe toxemia
- Moderate/severe dyspnea, disproportionately more than lung signs, e.g. crepts/ronchi
- Signs of distant lesions, e.g. hepatosplenomegaly, meningitis (30%), etc.

Diagnosis of miliary tuberculosis rests on characteristic X-ray, i.e. diffuse fine (<2–3 mm) miliary mottling (*snowstorm appearance*) and/or extrapulmonary disease. D/D of similar X-ray findings includes *Pneumocystis carinii* pneumonia, tropical eosinophilia, Loeffler syndrome, pulmonary hemosiderosis and fungal infections of lung.

Disseminated tuberculosis refers to relatively more insidious form of hematogenous or lymphatic spread of infection, characterized by symptomatic or asymptomatic involvement of at least *two non-contiguous sites, i.e. either pulmonary and one extrapulmonary or two extrapulmonary*

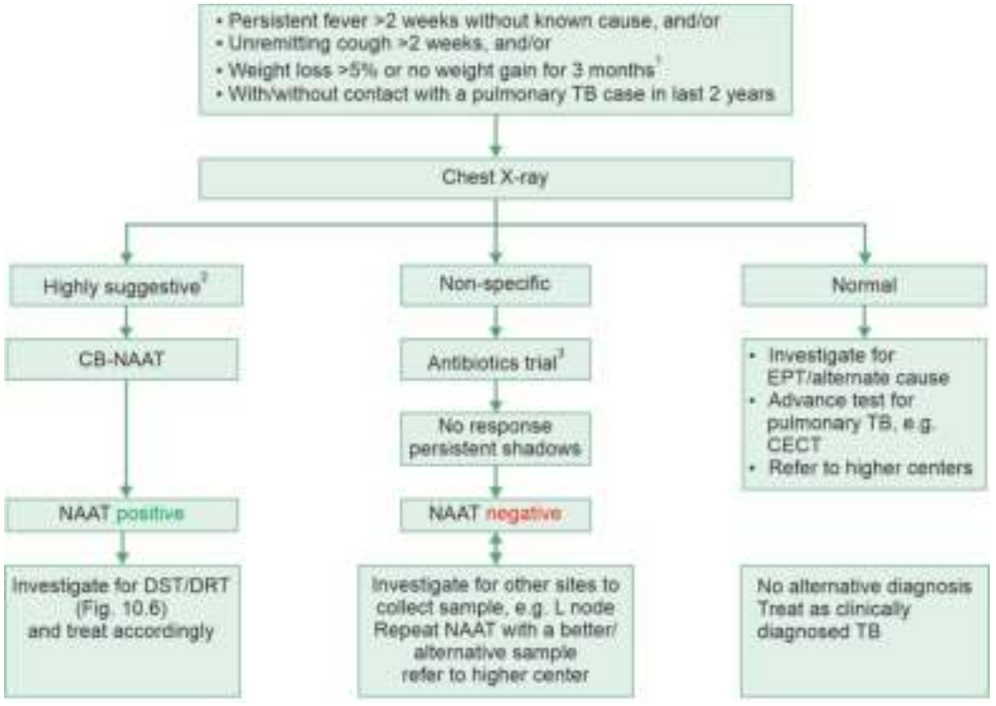

Fig. 10.3: Diagnostic algorithm for pulmonary tuberculosis in children.

[1]despite adequate nutrition or failure of nutritional rehabilitation in SAM children
[2]miliary, cavitatory or hilar/paratracheal lymphadenopathy
[3]for seven days (Amox/Co-amox), skip this step if already received
NAAT: Nucleic acid amplification test

sites. Most cases manifest after 3–5 years of primary infection due to slow evolution of extrapulmonary lesions.

Extrapulmonary tuberculosis (EPT) may be due to: (i) *hematogenous* spread during bacteremia, (ii) *lymphatic* spread via connecting channels, e.g. cervical/abdominal lymphadenopathy, or (iii) *direct spread* to adjacent tissues, e.g. rib or spine. While EPT may involve any organ, important lesions include: (a) *early* EPT with CNS or GIT disease, and (b) *late* EPT after 4–5 years with osteoarticular, genitourinary or skin disease. Common forms of EPT in children, e.g. lymphadenitis, meningitis, osteoarticular or abdominal disease have been discussed in respective chapters.

In NTEP, EPTB refers to:

- Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, including pleura, peripheral lymph nodes, abdomen, genitourinary tract, skin, joints and meninges.
- *Severe EPTB* refers to neurotuberculosis in all age groups and other forms of EPT in children <15 years (except peripheral or mediastinal lymphadenopathy without signs of compression).

Diagnosis: Detection of *M. tuberculosis* on direct smear or culture from infected body fluids/tissues, e.g. sputum, CSF, etc. is the *gold standard* for diagnosis, though yield is poor in children due to difficulties in specimen collection and paucibacillary nature of disease.

TABLE 10.19: Diagnostic tools in tuberculosis

Supportive	*Confirmatory*
• **TT/IGRA** • **Radiodiagnosis** X-rays USG, CT/MRI • **Biochemistry** Exudative body fluids ADA/TSA levels • **Histopathology** Aspiration cytology Tissue biopsy	• **Bacterial diagnosis** Direct smear (Ziehl-Neelsen stain) Solid culture: LJ Media Liquid culture: BACTEC, MGIT • **Molecular diagnosis** CB-NAAT (x-pert Mb) Line probe assay (LPA)

TT: Tuberculin test, **IGRA:** Interferon Gamma Adenosine deaminase (ADA) and tuberculostearic acid (TSA)

NTEP 2022 has proposed a diagnostic algorithm for diagnosis of PTB in children **(Fig. 10.3)** as well as for some other types of EPTB. Diagnosis in microbiologically negative cases must be made cautiously, supported by clinical or epidemiological indicators as well as indirect investigations **(Table 10.19)**.

- **Clinical suspicion** is the key for early diagnosis of TB, based on: (a) history of contact with sputum-positive case, (b) absence of BCG vaccination, (c) presence of malnutrition, (d) poor socioeconomic status with overcrowding, and (e) suggestive clinical picture.

TABLE 10.20: Common radiological features in TB

Mediastinal lymph nodes with ill-defined lung shadow
- Primary complex
- Progressive P. complex (large lung shadow)

Localized homogenous opacities
- Consolidation (large segmental, trachea central)
- Collapse (trachea > same side)
- Cavity (round/coin lesion, air/fluid level +)
- P. effusion (trachea > opp. side, obliterated CP angle)

Non-homogenous opacities
- Bronchopneumonia (large, irregularly distributed)
- Miliary (tiny, bilateral, uniformly distributed)
- Bronchiectasis (segmental honey-Coomb lesion)

Hyperleucent lesions
- Pneumothorax (trachea > opposite side, no BVM)
- Emphysema (trachea normal, BVM +)

BVM: Bronchovesicular markings

According to NTEP 2022 guidelines, Children with presence of any one of the following three clinical indicators are considered as ***Presumptive Pediatric Tuberculosis***, with/without history of contact in preceding 2 years:
- Persistent fever for > 2 weeks without a known cause
- Persistent cough for > 2 weeks, and/or
- Weight loss of >5% or no weight gain for >3 months, despite adequate nutrition and no apparent cause.

- **Radiological diagnosis:** Chest X-ray is the base-line investigation in children with presumptive PTB, **(Table 10.20)** interpreted as follows:
  - *Chest X-rays highly suggestive of the PTB* include those with: (a) miliary pattern, (b) hilar or paratracheal lymphadenopathy with/without parenchymal involvement, and/or (c) fibrocavitary lesions **(Fig. 10.4)**. All presumptive cases with these radiological patterns are considered as probable cases and should be subjected to bacteriological confirmation. Even if microbiologically negative, these children may be treated as ***clinically-diagnosed tuberculosis,*** after exclusion of alternative causes. Specificity of diagnosis increases with positive TST or history of contact in preceding two years.
  - *Chest X-rays with other lesions*, e.g. consolidation, non-homogenous shadows or bronchopneumonia, etc. are considered as non-specific **(Fig. 10.4)**. They must receive a 7-days course of antibiotics before repeat skiagram. Cases without improvement on repeat X-ray should be tested bacteriologically and if negative, need further evaluation to exclude other causes.
  - *Normal chest X-ray* practically rules out the pulmonary disease and child must be assessed for EPT *or* alternate causes *or* referred to higher center for further assessment.

  Other imaging investigations, e.g. USG, CT/MRI and bone scans are useful to delineate the extent of pulmonary or extrapulmonary disease.

- **Bacteriological diagnosis** is the gold standard for diagnosis with choice of specimen depending on the site of tubercular lesion. As sputum collection is difficult in young children: (a) early morning *gastric aspirate* after overnight fasting, (b) *induced sputum* after 3% saline nebulization and chest percussion, or (c) *bronchoalveolar lavage* is advised. Bacteriological diagnosis depends on:
  - ***Direct smear exam*** for AFB in sputum or other body fluids by conventional *Ziehl-Neelsen* staining **(Table 10.21)** or more sensitive fluorescent *fluorochrome* staining may also be used for rough quantitative assessment of bacillary load (1+, 2+, 3+). Smears are frequently false negative in children due to paucibacillary disease, specially if bacillary load is <10,000 bacilli/ml. Yield may be enhanced by centrifugation of specimen. Presence of AFB on smear is highly suggestive but cannot differentiate *M. tuberculosis* from other acid-fast organisms.
  - ***Bacteriological cultures*** are more sensitive with detection threshold of ~10 bacilli/ml. Cultures also allow species-identification and drug sensitivity testing (DST).
    - *Conventional* cultures using solid *Löwenstein-Jensen* media take longer time, i.e. about 3–6 weeks for isolation of organisms and another 2–4 weeks for DST and hence, have been gradually replaced by.
    - Rapid liquid-culture methods, e.g. automated radiometric culture assay (BACTEC) or myco-bacterial growth indicator tube (MGIT) systems, which allow isolation of organisms in 1–3 weeks and DST in further 3–5 days.
    - *Mycobacterial growth indicator tubes (MGIT)* is a rapid culture technique in which culture tubes have oxygen-sensitive fluorescent compound at the bottom. Initially, large amount of dissolved oxygen in media quenches emissions from the compound. Later, actively respiring mycobacteria consume the oxygen and allow the fluorescence to be detected by automated instruments.

- **Molecular diagnosis** is as reliable as bacteriological diagnosis, involving detection of mycobacterial DNA using cartridge-based nucleic acid amplification tests (CBNAAT) or Line probe assays (LPA).
  - ***Cartridge-based nucleic acid amplification test*** or CBNAAT (Xpert-RIF or Truenat) is the first test of choice for confirmation of diagnosis under NTEP guidelines due to rapid results (1–3 days) and ability to detect very low bacterial load, with sensitivity and specificity of >95% in smear-positive and 40–70% in smear-negative cases.

  However, CBNAAT cannot differentiate living from dead organisms in treated cases and contamination of samples by blood or pus may lead

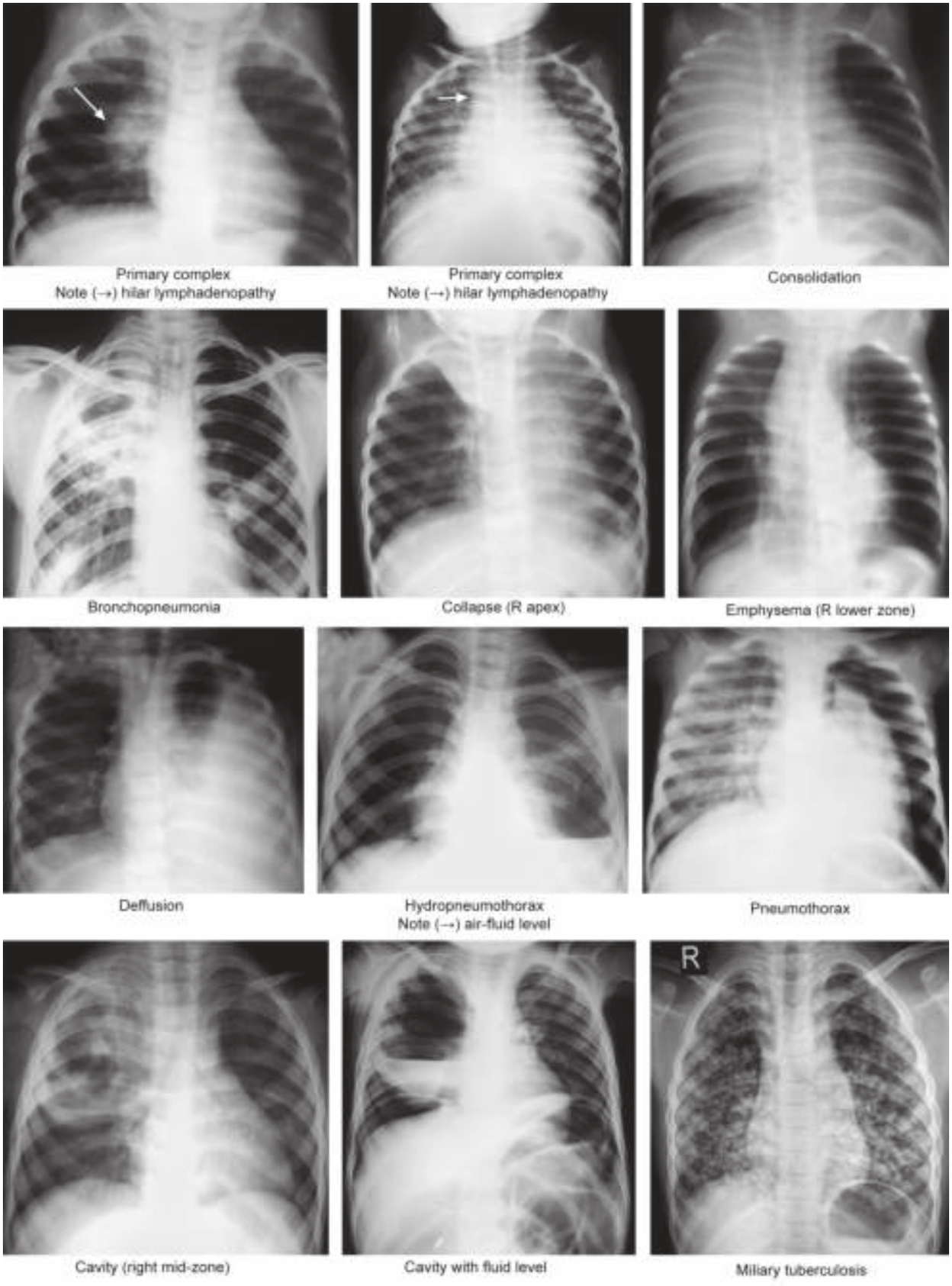

Fig. 10.4: **Common X-ray findings in pulmonary tuberculosis.**

TABLE 10.21: Ziehl-Neelsen staining for AFB - method

- Dry the slide (15–30 minutes) and fix over a flame
- Cover with carbolfuchsin and heat till vapours rise
- Leave for 5 minutes, then rinse in running water
- Stain with 25% sulfuric acid (2–4 minutes), then rinse
- Stain with 0.1% methylene blue (30 seconds), then rinse
- Examine under high power and oil immersion

to false-positive or false-negative results. CBNAAT also detects the presence of Rifampicin resistance (RR-TB), which is often used as a proxy for multi-drug resistance disease (MDR-TB).

– ***Line probe assay (LPA)*** are molecular tests to detect MTb complex and rapid diagnosis of Rifampicin and INH resistance by *first-line LPA* (LPA-FL) and resistance to fluoroquinolones and other second-line drugs by *second-line LPA* (LPA-SL). LPA needs many DNA copies (>10,000 per ml) for detection and can be used only on smear-positive or culture isolates with processing time of ~72 hours each for both LPA-FL and LPA-SL.

In NTEP, LPA-FL is indicated in all cases of confirmed tuberculosis and LPA-SL in cases of RR-TB or or INH resistance.

- **Histopathological diagnosis** is commonly used to confirm the diagnosis of EPT, using fine needle aspiration cytology (FNAC) or biopsy of the suspected lesion, showing presence of *chronic inflammatory infiltration, giant cells and caseation.* These specimens should also be used for microbial diagnosis and drug sensitivity/resistance testing.
- **Tuberculin sensitivity test (TST)** is a simple, widely used test to detect latent tuberculosis based on the presence of delayed type of hypersensitivity (DTH) against tuberculosis—an indicator of prior natural infection or BCG vaccination.

Tuberculin is a protein suspension of *M. tuberculosis*, available as purified protein derivative (PPD), with antigen load denoted as test units or TU (1 TU = 0.00002 mg PPD). Considering variable potencies of PPD derived from different strains, WHO recommend use of a standardized PPD-S, derived from *RT-23 strain* and stabilized with an additive *Tween 80. In India, 2 TU of PPD-S is recommended for TST.*

Mantoux test (MT) is the commonly used method for TST (others include *heaf test* or *tine test),* done and interpreted as follows:

– 0.1 ml of PPD-S (2 U) is administered intradermally using a TT syringe on volar aspect of forearm to raise a wheal of ~5–8 mm at the site of injection. This wheel subsides in 15–30 minutes and no reaction is visible locally for next 6–8 hours. In presence of DTH either due to previous natural infection or BCG vaccination, a local induration appear after 6–8 hours and peaks at 48–72 hours, associated with erythema.

Fig. 10.5: Tuberculin (Mantoux) test.

– Size of this induration (not erythema) should be read after 48–72 hours (up to 7 days), by a ball-point method, in *transverse direction* **(Fig. 10.5)**.

– An induration of 10 mm is considered as positive (5 mm in HIV infected), suggestive of *previous natural infection*. BCG is unlikely to produce an induration of >5 mm.

– *Diagnostic errors* in TST include:

▪ *False negative TST* in: (1) severe disease, e.g. military tuberculosis or tubercular meningitis, (2) severe malnutrition, (3) infection-induced anergy-up to 3 months after pertussis or measles, (4) immunocompromised states, e.g. HIV, (5) recent infection, as TT conversion takes 2–3 months after infection, (6) technical errors, e.g. inactive tuberculin, subcutaneous injection, etc.

▪ *False positivity* is rare, due to: (1) use of higher PPD strength for testing, (2) presence of non-tubercular mycobacterial infections, e.g. atypical mycobacteria or leprosy, and (3) secondary infection at the site.

– TST *alone should not be used for diagnosis of tuberculosis but only to support the diagnosis of: (a)* latent TB, (b) bacteriologically negative cases. It is also used to – (c) test the success of BCG vaccination, (d) identify the need for BCG vaccination in older TST-ve children, and (e) measure the prevalence of infection in the community.

– A new C-TB test to detect tuberculin skin sensitivity is in pipeline, which is not affected by prior BCG vaccination.

- **Interferon gamma release assay (IGRA),** commercially available as *TB quantiFERON gold®* or *TB Spot®* is an *in vitro* test to detect interferon (IFN)-gamma production by mononuclear cells in response to *M. tuberculosis* antigens. Like TST, positive IGRA test also indicates presence of TB infection but does not confirm the presence of disease. IGRA is expensive but unlike TT, does not require repeat visit for test reading or cross-react with BCG vaccination.
- **Biochemical investigations** are not diagnostic but may be used differentiate tubercular from pyogenic

etiology in EPT, e.g. CSF, ascites or pleural/pericardial effusions.

Tubercular exudate is characterized by: (a) straw-colour appearance, (b) cobweb formation on standing due to high fibrinogen content, (c) predominant lymphocytic leukocytosis, and (d) lesser elevation of proteins than in pyogenic exudate.

Other useful biochemical markers include presence of elevated *adenosine deaminase (ADA)* and *tuberculostearic acid (TSA) levels* in exudates—produced by degradation of lymphocytes and tubercular bacilli respectively.

- **Serodiagnosis** of tuberculosis involves detection of specific TB antigens (A60) or antibodies (IgM/IgG) in body fluids, though none of them differentiates infection from active disease and have *no role* in diagnosis of tuberculosis.

In NTEP 2022,

- ***Confirmed TB*** refers to a bacteriologically confirmed case on smear microscopy, culture or WHO recommended rapid diagnosis test, e.g. XpertMTB/RIF.
- ***Clinically diagnosed TB*** refers to a case, which is not bacteriologically confirmed but has been diagnosed as having active TB by a medical practitioner, who has decided to give full course of TB treatment. It includes cases dignosed on the basis of X-rays, suggestive history and extra-pulmonary disease without laboratory confirmation.
- ***Probable TB*** refers to at least one sign or symptom (unexplained fever, cough, weight loss) with chest X-ray consistent with tuberculosis ***and*** one of the following: (a) response to TB therapy, and/or (b) documented exposure and/or immunological evidence of TB infection.

Management of tuberculosis depends on the type and severity of the disease, DST and patient characteristics. For the sake of clarity, it has been discussed in following sections:

a. Anti-tubercular drugs
b. Anti-tubercular regimens
c. Supportive and symptomatic therapy
d. Monitoring and follow-up

A. Antitubercular drugs may be broadly divided into:

- ***First-line drugs*** are highly effective and least toxic, used in the majority of cases and include four drugs – Isoniazid (H), Rifampicin (R), Pyrazinamide (P), Ethambutol (E). Streptomycin is no longer used as first-line drug **(Table 10.22)**.
- ***Second-line drugs*** are less effective and more toxic, used only in cases with resistance to one or more first-line drugs. These drugs are classified in three groups, based on their efficacy and experience in treatment of drug-resistant cases **(Table 10.23)**. While all three drugs from Group A and one or two drugs may be included in second-line regimen, Group C drugs should be added only if Group A/B drugs cannot be used due to resistance or intolerance.

  Bedaquiline is the heart of second-line anti-tubercular regimen at present, except that it is not licensed for used in children below 5 years.

TABLE 10.22: First-line antitubercular drugs

Drug	*Dose (Range)* (mg/kg)*	*Side effects*
Isoniazid (H)	10 mg (7–15 mg)	Peripheral neuritis, hepatitis, psychosis
Rifampicin (R)	15 mg (10–20 mg)	Hepatitis, flu-like illness
Pyrazinamide (Z)	35 mg (30–40 mg)	Hepatitis, gout
Ethambutol (E)	20 mg (15–25 mg)	Optic neuritis

Maximum dose:* H 300 mg, R 600 mg, Z 2000 mg, E 1500 mg
All drugs given orally as single dose on empty stomach.

TABLE 10.23: Second-line antitubercular drugs

Group A *(Add All 3)*	Levofloxacin/Moxifloxacin (Lfx/Mfx) Bedaquiline (Bdq) Linezolid (Lzd)
Group B *(Add one or both)*	Clofazimine (Cfz) Cycloserine (Cs) or Terizidone (Trd)
Group C *(Add to complete the regimen and When Group A/B drugs Cannot Be Used)*	Ethambutol (E) Delamanid (Dlm) Pyrazinamide (Z) Imipenem-cilastatin (Ipm-Cls) *or* Meropenem (Mpm) Amikacin OR Streptomycin (Am/S) Ethionamide OR Prothionamide (Eto/Pto) p-aminosalicylic acid (PAS)

B. Antitubercular regimens: Multi-drug therapy is the cornerstone of anti-tubercular therapy, based on following considerations:

- Each case has different types of bacillary populations in the same lesion, including extracellular or intracellular organisms and slow-growing or rapidly-growing organisms. Some drugs act better on some bacillary sub-populations than others. H and R act best on fast-growing bacilli, Z on intracellular organisms and R on extracellular slow-growing bacilli.
- An effective drug regimen should use a mix of these drugs to attack all sub-populations of organisms. Ethambutol, though bacteriostatic drug with poor efficacy, is largely included in these regimens to prevent development of resistance to other drugs.
- An effective drug regimen should only include the drugs for which phenotypic sensitivity has been demonstrated on cultures *or* the resistance has not been detected on molecular testing. Indian data has shown maximum resistance to H (13%) followed by R (7%) and rarely to second-line other drugs (2–3%).

- An effective drug regimen should not contain less than four drugs at a time. In fact, drug-resistant cases usually need more than 5–6 drugs due to relatively less efficacy of second-line drugs.
- Since the emergence of drug-resistant mutations is higher in early stages of treatment due to higher bacillary load, antitubercular regiments are usually biphasic – including an:
  - *Intensive phase* (IP) to rapidly decrease the bacillary load, reduce infectivity and prevent deterioration and death, and a
  - *Continuation phase* (CP) to eliminate residual bacilli and reduce the risk of treatment failure and relapse. As fewer bacilli are left after IP, continuation phase usually needs fewer drugs.
- Since the dividing time of TB bacilli is ~21 hours, all drugs should be administered once a day, with no role of intermittent chemotherapy, unlike practiced earlier.

Universal Drug Resistance/Sensitivity Testing: NTEP 2022 recommends selection of appropriate drug regimen based on DST/DRT profile of cases, irrespective of previous treatment status (unlike previous protocols). All cases should be offered universal testing as per following algorithm **(Fig. 10.6)**:

- Two appropriate body fluid/tissue specimens should be collected from every patient and sent to laboratory in a cold chain – one for the CBNAAT and another for culture and sensitivity (preferably MGIT). EPTB samples should not be collected in formalin.
- Based on CBNAAT report, cases are divided into MTB detected (confirmed) or not detected (negative/presumptive). Confirmed TB cases are also further divided into – Rifampicin sensitive (RS-TB) or Rifampicin-resistant (RR-TB). If RR is detected with a very low level in a patient with low clinical suspicion, it should be confirmed on a repeat sample.
- All cases of RS-TB should be started on first-line regimen (discussed later) and tested by LPA-FL to confirm R-sensitivity and detect H-resistance. In case of LPA-FL showing:
  - H-sensitivity, continue with first-line ATT.
  - H-resistance, first-line ATT must be revised to H-mono/poly regimen, (discussed later) along with asking for LPA-SL.
  - Discordance with CBNAAT report in terms of R-sensitivity, CBNAAT should be repeated from another good sample.
- All cases of RR-TB should be subjected to LPA-SL to detect resistance to fluoroquinolones (Flq) and second-line injectable (SLI) drugs.
- Treatment should be initiated on the basis of LPA results, which may need to be modified later according to DST on liquid culture (LC-DST).

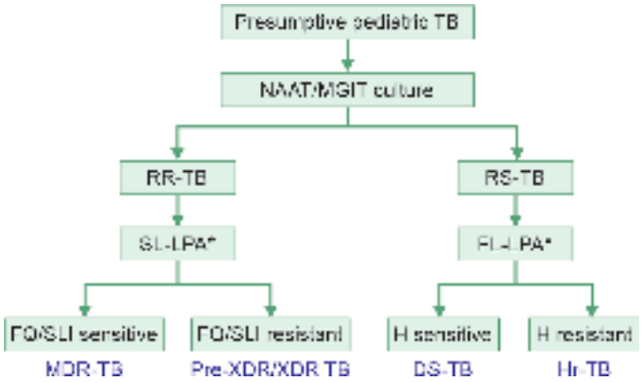

Fig. 10.6: Diagnostic algorithm for suspected drug resistant tuberculosis in children

*For discordance for RR between NAAT and FL-LPA, repeat NAAT at LPA laboratory

**Repeat NAAT in cases of RR-TB in a treatment-naive case

FL-LPA: First line-line probe assay, **SL-LPA:** Second line-line probe assay, for other abbreviations, *see text*

Drug Resistant Tuberculosis (Nomenclature): For the treatment purpose, all tuberculosis cases are classified on the basis of drug-resistance pattern, as follows:

- *Mono-resistant* (MR-TB), with resistant to one first-line drug only.
- *Isoniazid-resistant* (Hr-TB), with resistance to INH but susceptibility to RMP.
- *Poly-drug resistant* (PDR-TB), with resistance to more than one first-line drugs, other than both H and R.
- *Rifampicin resistant* (RR-TB), with resistance to R, with/without other drugs.
- *Multidrug-resistant* MDR-TB). With resistance to both H and R, with/without resistance to other drugs. *All cases of RR-TB are considered as H-resistant as well unless proved otherwise, hence, should be treated as MDR-TB.*
- *Pre-extensively drug-resistant TB* (Pre-XDR-TB), including MDR/RR-TB with resistance to fluoroquinolones (levoflox or moxiflox).
- *Extensively drug-resistant TB* (XDR-TB), including MDR/RR-TB with resistance to fluoroquinolone and at least one additional second-line drug from Group A, i.e. Bedaquiline and/or Linezolid.

Treatment Regimen: NTEP-2022 recommends following Regimens for Childhood TB, depending on DST/DRT **(Table 10.24)**:

- **First-line regimen** for All RS-TB (without H-resistance) including four drugs for 2 month of intensive phase and three drugs for 4 months for continuation phase **(2HRZE + 4 HRE)** with following considerations:
  - Continuation phase is extended to 10 months in cases of neurotuberculosis or spinal tuberculosis, with total duration of 12 months. (Intensive phase is not extended)

TABLE 10.24: TB treatment regimen as per DST/DRT

1. RS-TB with No H resistance	
All cases	2 HRZE +4HRE*
2. RS-TB with H mono/poly resistance	
All cases	(6**) Lfx R E Z (No intensive/maintenance phase)
3. RR/MDR TB (No FQ Resistance) (Non-extensive/Non-Diseminated PTB, Non-severe EPTB)	
Age >5 yrs/15 kg	**IP** (4–6 mo) Lfx, Cfz, Z, E, H^h, Eto, Bdq (6 mo) **CP** (5 mo) Lfx, Cfz, Z , E
Age < 5 yrs/15 kg (Shorter oral regimen)	**IP** (4–6 mo) Mfx^h, Km/Am, Cfz, Z, E, H^h, E **CP** (5 mo) Mfx^h, Cfz, Z , E
4. RR/MDR TB, but No FQ Resistance (Extensive/Disseminated PTB, severe EPTB)	
Age > 5 yrs/15 kg (Longer oral regimen)	(18–20) Lfx, Lzd, Cfz, Cs, Bdq (6 mo or more) (Replace Bdq with Dlm in children 6–17 years)
Age < 5 yrs/15 kg	Replace Bdq with any group C drugs
5. Pre-XDR TB with FQ Resistance	
Customized treatment with expert consultation	
6. XDR TB with Resistance to FQ + one more group A drug	
Customized treatment with expert consultation	

*Extent continuation phase to 10 months for Neuro/Spinal TB
**Extend to 9 months for extensive disease, uncontrolled co-morbidity, ExPT or any change in regimen due to resistance/intolerance. Extend to 12 months for Spinal and Neuro TB.
Ak: Amikacin; **Bdq:** Bedaquiline; **Cfz:** Clofazimine; **Cs:** Cycloserine; **Dlm:** Delanamid; **Eto:** Ethionamide; **FQ:** Fluoroquinlone **Hh:** High dose INH; **Km:** Kanamycin; **Lfx:** Levofloxacin; **MDR:** Multidrug-resistant; **Mfx:** Moxifloxacin; **IP:** Intensive phase; **CP:** Continuation phase

  - First-line regimen is also used for all: (a) cases with clinically-diagnosed TB or (b) cases who have been treated in the past even with history of treatment failure, default or recurrence, provided they are RS-TB at present.
  - Fixed-drug combinations (FDCs) are available under NTEP for first-line regimen and preferred due to simplified treatment and no risk of missing one or more of combination drugs.
- **H-resistant TB,** with/without resistance to other first-line drugs, should be treated with a monophasic regimen of four drugs **(6 LfxRZE)** for six months, i.e.: (a) replacing INH with Levofloxacin, and (b) no continuation phase.
- **RR-/MDR-TB** without resistance to second-line drugs should be treated with different regimens including second-line drugs depending on the severity of disease and age of the child **(Table 10.24)**. These regimens with higher pill burden and toxicity profile need longer duration of treatment. In case of intolerance to component drugs in second-line regimen, management has to modified in consultation with experts to decide the replacement sequence.
- **Pre-XDR/XDR TB** must be managed with tailor-made regimens in consultation with experts, replacing resistant drugs with group C drugs.

Probable or clinically diagnosed MDR-TB, with risk factors, e.g.: (a) close contact with a person having MDR-TB, treatment failure, death on treatment, (b) prior treatment with second-line drugs, and (c) no response to first-line regimen after excluding other cause of non-response, must also be managed in consultation with experts. In these cases, drug regimen is usually decided based on the drug sensitivity pattern of the likely source-case, if possible.

C. Supportive therapy includes adequate nutrition, management of co-morbidities, symptomatic treatment and treatment of complications, e.g. hydrocephalus, electrolyte imbalance, etc. Some specific issues in supportive management are as follows:

- ***Pyridoxine:*** Isoniazid interferes competitively with pyridoxine metabolism and may result in peripheral neuropathy. NTEP recommends pyridoxine supplementation (10 mg/day) to all children on INH-containing regimen.
- ***Steroids*** help in selected cases by reducing of excessive inflammatory damage and exudation, and facilitating intracellular penetration of drugs. Prednisolone (PO 2 mg/kg/day q8hr) is used for 2–4 weeks followed by gradual tapering only in: (a) tubercular meningitis, (b) military tuberculosis, (c) extensive endobronchial tuberculosis, (d) pericarditis, (e) large pleural effusion with distress and (f) immune reconstitution inflammatory syndrome (IRIS).
- ***Surgery*** may be indicated in large tubercular lesions to remove residual lesions after completion of antitubercular therapy, e.g. in lymphadenitis, segmental/lobar lung lesions or extrapulmonary tuberculosis.

D. Monitoring and follow-up: All children on ATT should be closely monitored for disease response, compliance and treatment, including clinical and laboratory follow-up. Clinical follow-up is advised even after completion of treatment for 2 years.

Clinical follow-up must focus on: (a) changes in clinical symptoms and signs, (b) physical examination, including weight record, (c) side-effects of medications, (d) adherence to treatment.

Laboratory investigations are needed only if indicated clinically, except repeat microbiological testing of respiratory secretions at the end of IP and CP, if possible. Liver function test are not routinely required without evidence of hepatopathy. Follow-up chest radiographs should be performed only at the end of therapy or earlier if no clinical improvement. Some important issues on follow-up are as follows:

- **Treatment interruptions** in the first-line regimen up to four weeks are managed by resuming the therapy, though missed doses of IP should be completed before starting CP and missed doses of CP should be completed by extending the duration of therapy.

However, in cases with longer interruption (>4 weeks), patient must be re-investigated for resistance profile, as in fresh case.

- **No-response or deterioration during follow-up**: All cases who do not respond satisfactorily or deteriorate on ATT are not due to drug resistance. Common causes of treatment failure include: (a) incorrect diagnosis in a clinically diagnosed case, (b) lack of adherence to therapy, (c) incorrect drugs or dosages, (d) inability to retain drugs, e.g. vomiting after medications, (e) comorbidities, and (f) paradoxical upgrading reactions, apart from drug resistance. All cases with poor response should be evaluated for these cases.
- **Paradoxical upgrading reactions (PUR)** refers to enlargement of existing lesions or unexpected appearance of new lesions during apparently adequate antitubercular therapy. These reactions usually develop after 3–12 weeks of the initiation of therapy and lasts for ~2 months before spontaneous resolution. PUR represent improvement of local immunity and accumulation of inflammatory exudates at previously small or invisible lesion and may present with new lesions or increase in size of existing lesions, e.g. lymph nodes, pulmonary infiltrates, pleural effusion, tuberculoma, etc. Lack of systemic symptoms suggests paradoxical reaction, though diagnosis should never be made without excluding DR-TB.
- **Drug-induced liver injury (DLI)** may develop in ~5% cases on first-line regimen, usually within first month of starting treatment due to three hepatotoxic drugs–INH, RMP and PZA. While routine liver function tests are not necessary, all suspected cases must be investigated for liver functions.

DLI is diagnosed in presence of any one of the following:

- >5 times elevation in AST/ALT values in asymptomatic patient,
- > 3 times elevation in AST/ALT values with > times elevation in bilirubin levels or
- Symptomatic patient.

Management of DLI includes withholding the offending drugs, e.g. RMP and PZA, and repeat LFT after a week. Withdrawn drugs are restarted in gradually increasing doses if AST/ALT drops < 2 times, in order of R followed by Z with AST/ALT monitoring every 3 days.

However, "*Hepatosafe*" therapy with alternative drugs is indicated in seriously sick patients with DLI, e.g. meningitis or military disease, using minimum three drugs – Streptomycin, Fluoroquinolone and Cycloserine.

In case of the recurrence of DLI, alternative treatment options with prolongation of treatment must be considered.

Prevention: Apart from public health measures to control airborne infections, important preventive measures to control TB in children include:

- Early detection and treatment of infectious cases,
- Airborne infection control practices,
- Contact screening and TB preventive therapy (TPT), and
- BCG vaccination.

TB preventive therapy (TPT) is indicated using single drug-INH PO 10 mg/kg/day (7–15 mg/kg/day range) in children <10 years and 5 mg/kg/day in older children (> 10 years) for 6 months, *after ruling out the active disease*, to all:

- All household contacts < 5 years of age of a bacteriologically confirmed PTB within past 3 months, irrespective of BCG or nutritional status,
- All household contacts > 5 years of age of a bacteriologically confirmed PTB, irrespective of the age, *if they are* positive on TT/IGRA.
- All HIV-infected children >1 year of age irrespective of the degree of immunosuppression, antiretroviral treatment or previous TB treatment.
- All HIV-infected infants <1 years of age, in contact with a pulmonary tuberculosis case.
- Babies born to mother diagnosed with tuberculosis during pregnancy.
- Other risk-groups individuals, e.g. those on immunosuppressive therapy, dialysis, planned for transplant, if they are positive on TT/IGRA.

TPT in contacts of MDR-TB, after exclusion of active disease depends on the sensitivity profile of contact case as follows:

- Contacts of RR-TB but FQ sensitive patients should receive TPI with Levofloxacin for 6 months (PO 15–20 mg/kg/day to max 75/mg/day).
- Contact of H-resistant R sensitive cases should receive RMP PO 15 mg/kg/day for 6 months (20 mg/kg/d above 10 years).

Congenital Tuberculosis

Congenital TB is not uncommon in Indian children though female sterility due to maternal genitourinary tuberculosis prevents many cases.

Mode of infection in these cases is either: (a) *transplacental infection* after placental lesion in mother (primary focus in liver), (b) *aspiration of infected aminotic fluid* (primary focus in lungs).

Clinically, congenital TB may be asymptomatic or presents as neonatal septicemia during 2nd–3rd weeks of life with fever, respiratory distress, hepatosplenomegaly, lymphadenopathy and meningitis (in 20–30%).

Diagnosis depends on maternal history of tuberculosis, placental examination for tubercles, clinical suspicion, neonatal chest X-ray and rarely, demonstration of AFB/

NAAT from gastric aspirate or bronchial lavage. TT is negative at birth in infected cases (but becomes positive by 2–3 months).

Management depends on clinical or radiological evidence of disease in the newborn. *Separation from mother and avoidance of breastfeeding to prevent postnatal infection is not recommended, even in sputum positive mothers.* NTEP/IAP recommends that:

- All babies born to tubercular mother should be breastfed, though mother should practice cough-etiquettes.
- All babies should receive BCG vaccinated at birth, without prior TST.
- Babies with normal chest X-ray at birth should receive TPT with single drug INH PO 10 mg/kg/day for 6 months with/without Pyridoxine, if mother is having RS-TB. TPT is not recommended if mother is having RR/MDR-TB.
- Babies with abnormal chest X-rays at birth, should be treated as per DST/DRT.
- Simultaneous treatment of mothers must be ensured.

Prevention of congenital TB largely depends on early diagnosis and treatment of disease in pregnant women. Streptomycin, due to risk of vestibular damage in newborn, is contraindicated during pregnancy.

National Tuberculosis Elimination Programme (NTEP)

National Tuberculosis Elimination Programme (NTEP) is the current version of Revised National Tuberculosis Control Programme (RNTCP, 1995), to fulfill the vision of *National Strategic Plan (NSP)*, i.e. to achieve "TB-free India" by the year 2025 (Five years ahead to global target in 2030).

Elimination refers to (a) achieve 80% reduction in disease burden, i.e. incidence and prevalence of disease <44 and <65/lakh population respectively, and (b) 90% reduction in mortality, i.e. <3/lakh population.

Objectives: NSP rests on four pillars of interventions- ***DETECT, TREAT, PREVENT, BUILD***. Accordingly, NTEP aims to:

- Achieve 90% notification rates
- Achieve 90% success rates for new cases and 85% for re-treatment cases
- To improve successful outcome of treatment of DR-TB cases
- To achieve decreased morbidity and mortality of HIV-associated TB
- To improve outcomes of TB care in private sector.

Operationally, NTEP is a centrally sponsored program under National Health Mission, managed by Central TB division, Ministry of Health and Family Welfare.

Activities: Some novel aspects of NTEP include:

- Screening of all cases with presumed TB disease, using standard screening **(Fig. 10.3)**
- Confirmation of diagnosis using standard algorithms and necessary investigations.
- Universal drug-resistance and sensitivity testing for all confirmed cases **(Fig. 10.6)**
- Standard treatment regimens, depending on resistance/ sensitivity profile **(Table 10.24)**
- Provisions for nutritional support and direct benefit transfer, to ensure compliance and manage co-morbidities.
- Use of Nikshya (NI- Nil, Kshya- TB) app – a web based information management system to ensure quality surveillance and monitoring.

10.14 LEPROSY

Leprosy (Hansen disease) is a chronic infectious disease, caused by *Mycobacterium leprae*. It mainly affects the peripheral nerves and skin, though upper respiratory tract, eyes, testes and other organs may also be involved.

While India achieved the target of leprosy elimination at National level in Dec 2005 with prevalence rate of < 1/10000 population, it still accounts for over half of the new leprosy cases in the world. About 7% of them are children <15 years of age. While there have been few reports of some resurgence in selected regions during 2021–22, National Health Mission aims to eradicate leprosy from India by 2027.

Epidemiology: *M. leprae* is an intracellular as well as extracellular acid-fast bacillus, present predominantly inhuman host.

Source of infection is usually a multibacillary open case, harbouring millions of organisms in nasal mucosa. Paucibacillary cases are intermittently infectious during exacerbations.

Mode of infection: Organisms are usually transmitted to susceptible host as droplet infection. Other modes of transmission, e.g. direct skin-to-skin contact, contaminated fomites, breast milk and via insect vectors, are extremely rare.

High-risk factors: Prolonged close contact with an index case is necessary for transmission. Infection in children is usually acquired from a family contact. *Other risk factors* include overcrowding, high humidity, social stigma preventing early diagnosis and immune status of the child.

Etiopathogenesis: All infected cases do not develop the disease and cell-mediated immunity (CMI) plays an important role in course of the disease. While in persons with high CMI, organisms are destroyed immediately on entry; progressive disease is produced in hosts with no or a little CMI. Most cases with moderate immunity develop a localized disease, e.g. *tuberculoid* or *indeterminate leprosy*, with acute exacerbations during periods of immunosuppression.

M. leprae multiplies very slowly, with long *incubation period* of ~ 3–5 years for lepromatous leprosy, though it is shorter in tuberculoid form.

Clinical spectrum spans from mildest indeterminate disease to most severe lepromatous leprosy (*see* classification below), with one or more of following cardinal features:

- *Skin lesions*, i.e. hypopigmented patches with/without loss of sensations. Loss of normal histamine induced flare response over hypopigmented patch is an early indicator of peripheral nerve damage, before detectable anesthesia.
- *Neurological lesions*, i.e. tender thickening of peripheral nerve trunks on palpation or nerve abscess formations with secondary anesthesia or parasthesia (tingling, crawling or pricking sensations). These lesions are best palpable over ulnar nerve behind the greater epicondyle or lateral popliteal nerve behind the lateral malleolus.
- *Secondary trophic changes*, e.g. neuropathic ulcers and deformities rarely appear in childhood and include facial deformities (nasal septal perforation, ear-lobule deformities, corneal ulcers) or limb deformities (wrist-drop, foot-drop, acral-ulcers, absorption of digits). Typical *leonine facies* with loss of eyebrows is uncommon in childhood.

Classification: According to *Indian classification*, leprosy is classified into five major types: (i) indeterminate, (ii) tuberculoid, (iii) borderline, (iv) lepromatous, and (v) neuritic disease. *WHO classify* leprosy as: (a) paucibacillary, single lesion, (b) paucibacillary (2–5 patches) and (c) multibacillary (6 patches).

- ***Indeterminate type*** is the earliest and least severe form, characterized by: (a) one or two flat hypopigmented macules, measuring 2–4 cm in size, with ill-defined margins, (b) nil or minimal loss of sensations over lesions, (c) negative smear and lepromin test. Most of these cases heal spontaneously, though 25–50% may progress to more severe forms.
- ***Tuberculoid leprosy*** is the commonest (50–60%) type in children, characterized by: (a) one or two large, raised erythematous papules or plaques (>10 cm) with well-defined margins, (b) definite loss of sensations over skin lesions, (c) thickening of regional nerve trunk, with/without formation of tender nerve abscesses, (d) negative smear but positive lepromin test and (e) granulomatous lesions (tuberculoid foci) on skin biopsy. Untreated cases remain stable for long time with intermittent exacerbations and increasing size.
- ***Borderline leprosy*** is a relatively ill-defined and unstable state, with frequent changes between tuberculoid (after treatment) or lepromatous (during immunosuppression) forms. Clinical features vary between two extremes of spectrum.
- ***Lepromatous leprosy,*** is most severe but rarest (<10%) type, with: (a) innumerable, confluent and *symmetrical* skin lesions, which begin as vague macules but turn papulo-nodular in late stages, (b) nil or minimal loss of sensations over lesions, (c) diffuse and often symmetrical sensory polyneuropathy, (d) positive smear but negative lepromin test, and (e) presence of vacuolated macrophages filled with *M. leprae* (*foam cells*) on skin/nerve biopsy.

  Untreated lepromatous cases may progress to develop trophic ulcers and deformities over years, while treated cases respond very slowly over 2–5 years with frequent recurrences. A combination of skin lesions (diffuse thickening of skin) and neuritic lesions (with loss of eyebrows and distortion of ear lobes) is responsible for typical *Leonine facies* in adults.
- ***Pure neuritic leprosy*** is very rare, characterized by tender thickening of multiple nerve trunks with sensory, motor and trophic changes in supplied area, leading to deformities and neuropathic ulcers, *without skin* lesions.

Diagnosis of leprosy in children depends on:

- ***Pathognomonic signs***, i.e. (a) hypopigmented lesion with loss of sensation, and (b) neural thickening and tenderness. Diagnosis of paucibacillary disease usually rests on clinical grounds only.
- ***Bacteriological confirmation*** **ons** Ziehl-Neelson staining of smears from skin lesions (*slit and scrape smear*) and nasopharynx. At least 6 slides should be prepared from each site and at least 200 fields should be examined before declaring the smear as negative.

  Bacterial index is calculated to assess the response to therapy after examining 7 smears-4 from skin lesions, one from nasal swab and 2 from ear lobes. Each smear is graded as per WHO criteria as negative, 1+, 2+ and 3+, followed by averaging of results to calculate bacterial index. Cases with bacterial index <2 are designated as paucibacillary while others as multibacillary lesions.
- ***Histopathological confirmation*** by skin or nerve biopsy to demonstrate granulomatous lesions is rarely required.
- ***Lepromin test*** measures the presence of CMI against *M. leprae*, using a refined antigen preparation, i.e. *Lepromin*. After intradermal injection of 0.1 ml of lepromin on forearm, reaction is read after 48 hours and after 21 days. *Early (Fernandez) reaction*, i.e. redness and induration of >10 mm after 48 hours, indicates previous infection by lepra bacilli. *Late (classical mitsuda) reaction* is taken as positive in presence of a nodule of > 5 mm on 21st day. Lepromin test is not diagnostic for leprosy but helps to classify the disease-strongly positive in tuberculoid leprosy and strongly negative in lepromatous variety.
- ***Serological tests,*** e.g. fluorescent leprosy antibody absorption tests (FLA-ABS test), RIA and ELISA are useful to detect subclinical infections, with high sensitivity and specificity.

TABLE 10.25: Anti-leprosy therapy in children (National Leprosy Eradication Programme)

Age	*> 10 years*	*< 10 years*
Multibacillary disease (3 drugs for 12 months)		
Rifampicin (monthly)	450 mg	10 mg/kg
Dapsone (daily)	50 mg	2 mg/kg
Clofazimine (monthly)	150 mg	6 mg/kg
Clofazimine (alternate day)	50 mg	1 mg/kg
Paucibacillary disease (2 drugs for 6 months)		
Rifampicin (monthly)	450 mg	10 mg/kg
Dapsone (daily)	50 mg	2 mg/kg

*Based on WHO schedules, which also includes single-dose therapy for single-lesion disease (Rifampcin 600 mg, Ofloxacin 400 mg and Minocycline 100 mg). However, it may be less effective than 6 months regimen.

- ***Molecular diagnosis*** with PCR testing is possible but rarely needed.

Management of leprosy includes:

- ***Specific antimicrobial therapy:*** Due to emergence of drug-resistance, current anti-leprosy therapy is essentially a *multi-drug therapy*, using three drugs-*bacteriostatic* dapsone and clofazimine and *bacteriocidal* rifampicin, in different regimens according to bacillary load **(Table 10.25)**. Therapy should continue for minimum 12 months in multibacillary and 6 months in paucibacillary disease or till smears are negative.
- ***Post-treatment surveillance:*** All cases should be followed clinically and bacteriologically, every year for minimum 2 years (paucibacillary) or 5 years (multibacillary disease), for relapses.
- ***Supportive therapy*** with: (a) prevention and treatment of trophic ulcers and deformities including reconstructive surgery, (b) vocational and social rehabilitation, (c) psychological support and (d) control of lepra reactions, discussed later.

Prevention: Reduction of infectious population by complete treatment is the mainstay of leprosy prevention in children. In an individual child with close family contact, following measures may be useful:

- *Chemoprophylaxis* with Dapsone (PO 1–4 mg/kg/week) for minimum 3 years or till index cases turns bacteriologically negative, has shown ~35–53% protection rate. Recently, long-acting *acedapsone* given intramuscularly every 10 weeks for 210 days, has shown ~ 78% protection.
- *Vaccine is not* available, though BCG is expected to provide ~30% protection against leprosy.

Lepra reactions, i.e. acute clinical exacerbation, usually after initiation of therapy are common (50%), and reflect sudden change in host's parasite immunological balance. Mainly two types of reactions are seen:

- *Type I (Reversal) reactions* are common in borderline leprosy, with acute swelling and tenderness over existing cutaneous and neural lesions, often leading to irreversible nerve injury with foot-drop, claw-hand, etc. These may be treated with PO prednisolone 1 mg/kg/d till response, followed by alternate day therapy to prevent relapse.
- *Type II (Erythema nodosum leprosum) reactions* occur in lepromatous leprosy, presenting with high fever, migratory polyarthralgia and tender erythema nodosum. These reactions may be treated with steroids, thalidomide or clofazimine.

National Leprosy Eradication Programme

National Leprosy Eradication Programme (1983) is the revised version of previous National Leprosy Control Programme (1955) that aims to eradicate leprosy from India by early case detection, multidrug chemotherapy, and disability prevention. Leprosy screening has been now integrated with Rashtriya Bal Swasthya Karyakram (RBSK) and Rashtriya Kishor Swasthya Karyakram (RKSK) for screening of children. National Health Mission aims to eradicate leprosy by 2027.

10.15 TETANUS

Tetanus is an acute life-threatening illness, characterized by painful muscular spasms and stiffness continues to be a significant cause of morbidity and mortality in children despite the availability of a safe and high effective vaccine for many decades.

However, *Tetanus neonatorum*, the severest form of tetanus in newborns has been eliminated from India since 15th May 2015.

Epidemiology: *C. tetani* is gram-positive *anaerobe*, present as spores in stools of various herbivores animals. These spores survive for many years in fecal-contaminated soil and cannot be killed by boiling, but easily by autoclave.

Tetanus spores from soil enter the body via: (a) contaminated wounds, usually a penetrating or crush injury, (b) perforated ear canal in otitis media (*otogenic tetanus*), (c) unsterilized needles/surgical instruments, and animal bites. Neonatal infection due to cord-cutting by unsterile blade/scissors is now extremely rare.

Pathogenesis: At the site of entry, the spores germinate, proliferate and produce a powerful exotoxin, i.e. *tetanospasmin*. Being strongly neurotropic, this toxin binds at neuromuscular junction and traverses along the axonal sheaths towards the spinal cord. In cord, it blocks the release of neurotransmitters in inhibitory spinal interneurons, leading to simultaneous agonist-antagonist muscular action, i.e. typical muscular spasms. The role of Tetanolysin – another exotoxin released in tetanus is unclear, perhaps contributing to produce anaerobic environment by damaging surrounding tissues.

Clinical manifestations range from localized or provoked *trismus* to generalized, severe, frequent and spontaneous muscle *spasms*. A typical case presents after *incubation period* of 5–15 days with three overlapping stages, as follows:

a. ***Stage of trismus*** (lock-jaw) is characterized by painful spasm of masseters with difficulty in opening the mouth, chewing and swallowing. For few days, it may be the sole manifestation or associated with signs of muscular rigidity, e.g. (i) *risus sardonicus*-a typical fixed-smiling face due to spasm of facial muscles, (ii) *abdominal rigidity*, and (iii) *opisthotonus*-spasm of back muscles with dorsally-curved posture **(Fig. 10.7)**.
b. ***Latent period*** is the time-lag between onset of trismus and appearance of spasms, usually not more than 2–3 days. Duration of latent period is inversely related to the severity of disease.
c. ***Stage of spasms*** is characterized by: (i) *reflex spasms*—sudden, painful tetanic contractions of voluntary muscles with hyperextension of limbs and back on slightest provocation, e.g. sound, touch, light or even wind movements, (ii) *spontaneous or unprovoked spasms* in severe disease, and (iii) *laryngeal spasms*—commonest cause of death in these children. Moderate fever and signs of autonomic imbalance, e.g. tachycardia and hypertension, are present in some cases.

As a rule, the sensorium remains normal even in severe or terminal cases of tetanus, unless clouded by hypoxia due to respiratory failure or other co-existing disease.

Other presentations include:

- ***Localized tetanus***—the mildest form with painful muscular rigidity and spasm around the site of injury, e.g. trismus in otogenic tetanus.
- ***Cephalic tetanus***—the rarest variant, with cranial nerve palsies, trismus, risus sardonicus, lid-retraction and spastic paralysis of tongue and pharynx, but *without* generalized muscular rigidity.
- ***Neonatal tetanus*** usually presented from 3rd 14th day, with refusal to accept breastfeeds, gradually progressing to full-blown picture over few hours.

Complications result from: (a) mechanical injury due to violent muscle spasms, (b) airway obstruction due to laryngeal spasms, (c) autonomic disturbances, and (d) therapeutic procedures **(Table 10.26)**.

Diagnosis is mainly clinical, based on: (i) history of injury or otitis media, (ii) unimmunized status, and (iii) typical clinical features, e.g. trismus, spasms, etc.

Spatula test, i.e. clenching of teeth on insertion of a spatula into the patient's mouth, is useful to demonstrate mild trismus in doubtful cases, though should be avoided in an obvious case due to risk of oral mucosal injury.

While rarely required, diagnosis may be confirmed on wound cultures for *C. tetani*, positive in <40% cases.

Investigations are also indicated to: (a) identify concomitant infection at the site of entry, e.g. wound/ear-swab cultures, (b) detect serious complications and (c) exclude other causes of muscle spasms.

D/D includes: (a) *rabies* (history of dog bite, hydrophobia), (b) *strychnine poisoning* (extremely rare), (c) *meningitis* (abnormal sensorium/CSF), (d) *tetany* (carpopedal spasms), (e) *phenothiazine dyskinesia* (history of drug exposure, transient course) and (f) *pseudotrismus* due to painful conditions, e.g. dental or parapharyngeal abscess.

Treatment of tetanus aims to: (a) neutralize circulating exotoxin by antitoxin, (b) prevent further toxin production by local wound care and antibiotic therapy, (c) prevent muscular spasms, and (d) treatment of complications.

All cases need to be hospitalized irrespective of severity. Important steps in management are:

a. ***Nursing environment:*** The child should be nursed in a dark-quite room with minimum stimulation, as even slight light/sound may stimulate painful spasms.
b. ***Wound care*** with cleaning and debridement of dead tissue to prevent anaerobic conditions that favour clostridial growth. Though cultures are usually negative for clostridia, wound/aural cultures should be collected to identify secondary infections.

Fig. 10.7: Tetanus: (A) Trismus; (B) Ophisthotonus.

TABLE 10.26: Complications of tetanus

Mechanical injuries:
- Tongue or lip injuries
- Compression fractures bones, e.g. spine
- Muscle fractures and/or rhabdomyolysis

Airway obstruction due to laryngeal spasms
- Sudden choking and death
- Aspiration pneumonia

Autonomic disturbances
- *CVS:* Hypertension/hypotension, arrhythmia
- *GIT:* Paralytic ileus, acute gastric dilatation

Iatrogenic complications
- *Over-sedation:* Apnea or respiratory failure
- *Nursing-related:* Bed-sores, aspiration

c. ***Passive immunization*** with human tetanus immunoglobulin (TIG), as soon as possible to prevent fixation of exotoxin at peripheral neuromuscular junctions. Optimal dose of TIG is not established, ranging 3000–6000 IU, given intramuscularly. Intrathecal TIG is no longer recommended.

d. ***Antibiotics*** to arrest further growth of clostridia and production of antitoxin, as well as to prevent secondary infections. Metronidazole (IV 30 mg/kg/d q6hr) is the preferred choice than conventional penicillin, which is a GABA-antagonist like tetanus toxin and can accentuate spasms.

e. ***Active immunization*** with a single dose of TT/Td (0.5 ml deep IM) is indicated in all cases on admission to initiate active antibody formation, irrespective of previous immunization status.

f. ***Sedation*** is cornerstone of symptomatic therapy in tetanus, to prevent and control the spasms. Level of sedation has to be adjusted according to severity of disease. Mild cases without spasms may be treated with single drug, i.e. diazepam, given orally via intragastric tube or per-rectally. However, severe cases require either high-dose monotherapy (oral or IV diazepam) *or* multi-drug sedation (additional drugs, e.g. phenobarbitone and/or chlorpromazine).

A general practice is to start with a single drug-diazepam IV (0.1–0.2 mg/kg every 3–6 hr) and gradually increase the dose, till spasms are controlled or safe-limit is reached. *In controlled cases*, IV therapy may be substituted with oral preparation via intragastric tube. *In uncontrolled cases*, additional drugs may be added gradually in increasing doses. Some basic rules of sedation therapy are:

- Parenteral sedation is risky than oral therapy and should be used only for initial control or in severe cases.
- Drug-doses should be increased gradually, but never to exceed safe-limits.
- IV bolus of sedatives should be given very slowly, to avoid sudden respiratory depression.
- When multiple drugs are used, simultaneous administration should be avoided. Schedule must be tailored to provide round-the-clock sedation.
- Sedation is gradually tapered after the patient is spasm-free for minimum seven days.
- Occasional breakthrough spasms in a controlled case are not uncommon, which may be treated with additional doses of IV diazepam (0.2–0.5 mg/kg).

IV magnesium sulphate has been used as an adjunctive drug to reduce the doses of benzodiazepines with added benefit of controlling autonomic symptoms. Magnesium is a pre-synaptic neuromuscular blocker, which blocks the release of catecholamines from nerves and reduces receptor responsiveness to released catecholamines. Hypotension and respiratory depression are major adverse effects of magnesium therapy.

g. ***Muscle relaxants***, e.g. *pancuronium* or *anesthesia* with ventilatory support may be required in refractory cases to maximize sedation. Other muscle relaxants, e.g. baclofen, if required, should also be used only in intensive care settings.

h. ***Supportive care*** includes: (i) Adequate nutrition via nasogastric tube or IV, (ii) airway maintenance with frequent suction and/or tracheostomy, (iii) breathing support with oxygen/assisted ventilation, (iv) back, bowel and bladder care and (v) management of complications. Percutaneous gastrostomy may be used for feeding to minimize the risk of aspiration.

Outcome: Overall mortality is post-neonatal tetanus is 15–20%, usually due to laryngospasm or aspiration.

Outcome is poor in—(a) younger children, (b) shorter incubation period (<7 days), (c) shorter latent period (<48 hours), (d) higher frequency and duration of spasms, (e) presence of autonomic disturbances, (f) concomitant complications, e.g. aspiration and airway obstruction and (g) quality of nursing care and sedative therapy. *Patel and Jog criteria* may be used to assess the severity of tetanus **(Table 10.27)**.

In survivors, long-term sequelae, e.g. cerebral palsy, mental retardation and behavioral problems, are not uncommon due to hypoxic brain damage during spasms.

Prevention of tetanus includes:

- *Active immunization* with three doses of primary immunization at 6, 10 and 14 weeks and boosters at 18 months and 5 years (DTwP or DTaP), followed by Td at 10 years of age and subsequently at every 10 years (TT). IAP recommends a single dose of Tdap at or after 7 years of age, followed by Td every 10 years (Ch 9.2.1). Antenatal immunization of mothers with two doses of Td at 4 weeks interval, starting in early

TABLE 10.27: Modified Patel and Jog criteria for severity of tetanus

a. Rigidity of muscles	
Neck	1
Abdomen	1
Limbs	1
Trismus	1
b. Duration of each spasm	
< 1 hour	2
> 1 hour	4
Laryngospasm	6
c. Autonomic changes	
Temperature > 38°C	2
Heart rate > 120/min	2
Respiratory rate > 40/min	2
Severity score:	
< 3 (mild), 3–10 (moderate), > 10 (severe)	

pregnancy (single dose in subsequent pregnancies) is vital to prevent neonatal tetanus.

- *Prevention of spore-entry* by immediate wound care, treatment of otitis media, trained obstetrical care, etc. Safe delivery practices include cord-cutting by sterile blade with no subsequent contaminated dressings.
- *Passive prophylaxis* with tetanus immunoglobulin (TIG) is indicated in: (a) potentially infected severe wounds with incomplete or unknown previous immunization status, (IM 5000 IU) within 3 days of injury, and (b) babies born to unimmunized mothers (IV 250–500 IU), within 6 hours of birth. Anti-tetanus serum of equine origin (ATS) is no longer recommended due to serious side effects.
- *Post-injury TT immunization* schedule depends on previous immunization status **(Table 10.28)**; using any age-appropriate tetanus containing vaccine (DPT/Tdap/Td/TT).

Other important clostridial infections in children are as follows:

Pseudomembranous colitis (PMC): It is an acute dysentery-like illness, due to overgrowth of pathogenic *C. difficile* or *C. perfringes* in gut.

Pathogenesis: Preceding antibiotics therapy (specially ampicillin) is most important risk factor for PMC, which damages normal gut flora to facilitate clostridial growth. Pathogenicity of these strains is mediated by production of two toxins—toxin A (enterotoxic) and B (cytotoxic).

Clinically, most cases present with mild self-limiting diarrhea, but a typical case presents with bloody dysentery and passage of pseudomembranes (mucosal sloughs) in stools. Constitutional features, e.g. fever, abdominal cramps and vomiting are common.

Diagnosis must be suspected in a case of diarrhea or abdominal pain, who is on antibiotics *or* has received them in last 2 months. Confirmation requires: (a) detection of *C. difficile* toxin in stools by immunoassay, *or* (b) colonoscopy to visualize pseudomembranous plaques.

Treatment includes: (a) discontinuation of suspected antibiotics, (b) fluid and electrolyte correction, and (c) specific therapy with metronidazole (PO 20–40 mg/kg/d q6hr) or vancomycin (IV 40 mg/kg/d q6hr) for 7–10 days. *Vancomycin is the only antibiotic, not known to cause PMC*. Although most cases respond well, recurrence is common.

TABLE 10.28: Post-injury immunization for TT**

Immunization Status	*TIG*	*TT*
Fully immunized		
Minor injury	No	TT/Td if >10 years lapsed
Major Injury	No	TT/Td if >5 years lapsed
Unimmunized/Partially immunized		
Minor injury	No	DTwP/DTaP/TdaP/Td*
Major injury	Yes	DTwP/DTaP/TdaP/Td*

*Followed by remaining doses for catch-up immunization

Botulism is a rare but potentially fatal disease with acute flaccid paralysis, due to a *neurotoxin,* produced by some strains of *C. botulinum*.

Pathogenesis: Spores of *C. botulinum* are ubiquitously present in soil, which may germinate *in vivo* (wounds) or *in vitro* (foods), under anaerobic conditions to produce a highly potent neurotoxin. According to the mode of infection, botulism may be divided into 3 distinct types:

a. *Infant botulism* due to ingestion of contaminated honey (as pre-lacteal feed) is often fatal, unless recognized and treated promptly.
b. *Food-borne botulism* due to ingestion of pre-formed toxin, present in spore-contaminated foods, e.g. home-canned or low-acid foods (sauces). Heating for 5 minutes destroys the pre-formed toxin.
c. *Wound botulism* due to *in vivo* germination of spores, multiplication of organisms and toxin production in infected wounds with dead tissue, e.g. crush injuries. Toxin spreads hematogenously to reach synaptic sites and block neuromuscular transmission.

Clinical presentation: Incubation period is shorter in food-borne or infant botulism, due to pre-formed toxins (18–36 hours), as compared to wound botulism (4–10 days).

Acute symmetrical descending flaccid paralysis is the cardinal feature of botulism, beginning with oculobulbar involvement, e.g. diplopia, ptosis, dysphagia, dysarthria and dysphonia and rapidly progressing downward to involve all muscles, including respiratory paralysis. In infants, weak cry and reduced spontaneous movements may be the first manifestation. Sensorium is normal, except in terminal cases due to hypoxia.

Other important features resemble atropine poisoning (anti-parasympathetic activity) with dry mouth, constipation and absence of sweating.

Outcome is poor in severe cases with death due to respiratory failure. Mild cases recover completely.

Diagnosis is suggested by: (a) *typical clinical picture*, i.e. descending flaccid paralysis with normal sensorium, and (b) *characteristic EMG findings*—brief, small, abundant motor-unit action potential in infants *or* potentiation of evoked muscle potential at high frequency in older children.

Confirmation requires: (a) *detection of toxin* in serum, wound site or feces, *or* (b) positive *wound culture.*

Management includes: (a) *supportive* therapy including ventilatory assistance, (b) *debridement* of dead tissue in contaminated wounds, (c) *anti-toxin infusion* (equine/

human, not freely available), and (d) *antibiotics* (in wound-botulism only) to control bacterial proliferation and further toxin production.

Aminoglycosides, which have neuromuscular toxicity, are contraindicated. *Antibiotics are not recommended for food-borne or infant botulism,* except to cover secondary infections.

Gas gangrene is rapidly progressive infection of soft tissue due to *C. perfringens*, with severe edema, necrosis, crepitations and a characteristic sweet odor in serosanguineous discharge. Pain is typically disproportionate to appearance of wound and systemic complications, e.g. shock and renal failure, develop rapidly.

Early debridement of wound with excision of necrotic tissue, IV antibiotic therapy with high-dose penicillin *or* clindamycin, and hyperbaric therapy (controversial role) may be life saving, but prognosis is poor.

10.16 NON-CLOSTRIDIAL ANAEROBIC INFECTIONS

Anaerobic infections may be classified according to their microbial characteristics **(Table 10.29)** or oxygen tolerance, i.e. *obligate* and *facultative* anaerobes. Of these, clostridial infections have already been discussed in previous Ch 10.15.

Non-clostridial anaerobes are common colonizers of human flora and disease is usually caused by proliferation of endogenous flora in anaerobic conditions. Clinical disease due to these infections is often non-specific and remains localized to colonized sites, e.g. GIT, respiratory tract, ears, sinuses, etc.

High-risk factors for non-clostridial anaerobic infections include: (a) crush injuries with devitalized areas and reduced oxygen tension, (b) co-existing aerobic infection to utilizes oxygen, and (c) defective mucosal clearance, e.g. poor hygiene, aspiration and unconscious child.

Clinical spectrum of non-clostridial anaerobic infections is extremely wide, **(Table 10.30)**, though some unique presentations are as follows:

- ***Vincent angina*** *(trench mouth)* is an acute, fulminant, necrotizing infection of oral cavity, characterized by painful ulcers, mucosal swelling, foul breath and pseudomembrane formation.
- ***Ludwig angina*** is life-threatening cellulitis of sub-lingual and sub-mandibular spaces, characterized by sudden onset of tender neck swelling (*bull-neck*) and respiratory difficulty due to airway compression.
- ***Noma neonatorum*** **(cancrum oris)** is a rare serious anaerobic infection in newborns and severely malnourished infants; characterized by acute, rapidly progressive gangrene of buccal mucosa that rapidly progress to form perforating cheek ulcer. Secondary Pseudomonas infection is common. Diagnosis is clinical and therapy includes intensive antibiotic therapy. Reconstructive plastic surgery may be needed in survivors.

Diagnosis of anaerobic infections depends on clinical suspicion and proper cultures. Anaerobic cultures should be collected from aspirates, abscesses or biopsies, and not from superficial sites of colonization, e.g. throat or stools. Cultures should be transported immediately to laboratory in specific transport media, which facilitates anaerobic growth.

Anaerobic cultures are indicated in presence of: (a) foul-smelling putrid odor, (b) severe tissue necrosis, gangrene or deep abscesses, (c) wound crepitus, (d) sterile aerobic cultures despite poor therapeutic response, and (e) clinical states compatible with anaerobic infections.

Treatment of these infections requires adequate drainage of the site with removal of dead tissue and appropriate antibiotic therapy with either: (a) Metronidazole *or* clindamycin in milder cases or (b) Carbapenem *or* imipenem *or* ampicillin+sulbactum in severe cases.

TABLE 10.29: Classification of anaerobic infections

Gram-positive bacilli
Clostridium tetani, C. botulinum, C. perfringens
Lactobacillus. Bifidobacterium
Gram-negative bacilli
Bacteroids, fusobacterium
Gram-positive cocci
Peptostreptococci, peptococci
Gram-positive cocci
Veillonella

TABLE 10.30: Common non-clostridial anaerobic infections

Oro-pharyngeal *(poor oral hygiene)*
Periodontal disease
Vincent angina *or* Ludwig angina
Peri-tonisllar abscess
Upper respiratory tract *(extension from oral flora)*
Chronic sinusitis
Chronic otitis or mastoiditis
Lower respiratory tract *(poor mucus clearance)*
Aspiration pneumonia
Lung abscess
CNS *(extension from otitis, mastoiditis)*
Brain abscess
Subdural/epidural empyema
Intra-abdominal *(extension from gut flora)*
Perforation peritonitis
Appendicitis, typhilitis
Necrotizing enterocolitis
Skin/soft tissue *(bites, penetrating/crush injuries)*
Cellulitis, fasciitis, myositis
Gas gangrene
Female genital tract *(poor hygiene, local extension)*
Vaginitis
Pelvic inflammatory disease (PID)
Chorioamnionitis and septic abortion (in pregnancy)

10.17 RICKETTSIAL FEVERS

Rickettsial diseases are primarily zoonotic infections, with humans infected accidentally. These infections are more common in adults, specially during the warm and humid season.

Incidence: While rarely diagnosed, four rickettesial infections, i.e. *scrub typhus*, *murine typhus*, *Indian tick typhus* and *Q fever* seem to be significantly prevalent in India **(Table 10.31)**. Scrub typhus is prevalent all over India; murine typhus and Q fever in north India; and Indian tick typhus fever in central India. Focal outbreaks of murine typhus occur in coastal cities, due to high rodent population at ports/docks.

Other rickettsial infections, e.g. epidemic typhus (*R. prowazekii*), Rocky mountain-spotted fever (*R. rickettsii*), rickettesial pox (*R. akari*) are rare in India, though prevalent in other parts of world.

Epidemiology: Rickettsiae are obligate *intracellular* bacteria that usually infect arthropods, e.g. ticks and mites, *or* other animals e.g. cattle and sheep. Human infection is acquired by: (a) bite of infected mite or tick (scrub typhus, Indian tick typhus), or (b) inhalation or contact with vector/animal excreta (murine typhus) or (c) ingestion of infected cattle products, e.g. milk (Q fever). Rickettsial diseases are more common in rainy and winter seasons and in rural population.

Pathogenesis of most rickettsial infections involves diffuse vasculitis leading to microvascular leakage and vascular lumen obstruction.

Clinically, most rickettsial diseases present after an incubation period of 1–2 weeks with: (a) sudden onset of high-grade fever with severe myalgia an headache; (b) Rash on day 2–5 of illness, which may be pruritic and petechial, usually involving palms and soles; (c) Eschar formation – a crusty necrotic lesion at the site of vector bite with or without regional lymphadenopathy. Q fever typically presents as acute pneumonia or influenza-like illness.

More serious manifestations may include aseptic meningitis or encephalitis, pneumonia, acute renal failure and acute gastroenteritis or surgical abdomen. Complications, e.g. DIC, ARDS, hemophagocytic lymphohistiocytosis, purpura fulminans, gangrene and myocarditis are not uncommon.

Diagnosis of rickettsial fever should be considered in any fever of > 5 days with suggestive epidemiological, clinical and laboratory indicators **(Table 10.32)**, after exclusion of other causes.

Diagnosis may be confirmed by polymerase chain reaction (PCR) or positive IgM ELISA test. *Weil Felix reaction* is a simple test with low sensitivity but good specificity, specially when higher titer cut-offs of > 1:320 are used. However, a single titre of > 1:80 also indicates possibility of infection.

Epidemiological confirmation is also possible on ELISA or immunofluorescence assay suggesting >4-fold rise in antibody titers after 2–4 weeks.

TABLE 10.32: When to suspect Rickettsial infections

Undifferentiated fever for > 5 days with .....

- **Suggestive epidemiological features**
  - Residence in endemic area
  - Presence of rodents/ticks in/around home
  - Visit to forests and farmlands
  - Animal sheds in proximity of homes
  - Contact with pet/stray dog infested with ticks
  - Similar cases in family, neighbourhood
- **Suggestive epidemiological features**
  - Dengue-like illness with rash, headache, myalgia
  - Eschar formation
  - Hepatosplenomegaly/lymphadenopathy
  - Acute menigoencephalitis
  - Community acquired pneumonia
  - Presence of GIT, liver or kidney involvement
  - Sepsis of unclear etiology
- **Suggestive laboratory features**
  - Normal/low leukocyte count with thrombocytopenia
  - Raised ESR and CRP
  - Others e.g. elevated hepatic transaminases

TABLE 10.31: Important Rickettsial infections in India

Disease	*Agent*	*Reservoir*	*Transmission*	*Clinical features*	*Prevention*
Scrub typhus	*R. tsutsugamushi*	Rat-mite	Mite-bite	Local eschar Prolonged fever Macular rash Lymphadenopathy	Rat control, Insecticide spray Personal protection
Murine typhus	*R.typhi*	Rat (Flea)	Contact[1]	Same, except eschar	Same
Indian Tick typhus	*R. conorti*	Dog-tick	Tick-bite	Same as *S. typhus*	Dog disinfection Avoid dog-contact
Q fever	*C.burnetti*	Cattle, sheep, ticks	Inhalation[2] Ingestion	Acute pneumonia influenza-like illness	Use pasteurized milk Cattle-shed sanitation

[1]contact or inhalation of rat-flea excreta.
[2]or contact with dust contaminated with animal excreta or ingestion of infected products, *e.g.* milk.

Treatment: PO/IV Doxycycline 100 mg BD (2.2. mg/kg in children <40 kg) for three days after defervescence or total 7 days, is the drug of choice for all rickettesial infections, which may be initiated without waiting for laboratory confirmation.

Doxycycline can be used in younger children as well since a short course will not lead to dental staining. Alternative drugs include Azithromycin (PO 10 mg/kg/d x 5 days), or Rifampicin (only in refractory cases). Response to treatment is dramatic and persistence of fever beyond 48 hours of therapy should alert about possibility of alternative or additional diagnosis. Treatment also includes other supportive measures including treatment of organ dysfunction.

Prevention of Rickettsial diseases depend on:

- *Control of reservoir/vector population*, e.g. Rodents (scrub typhus), insecticide sprays (Murine typhus) and disinfection of pet-dogs (Indian tick typhus), etc. and
- Avoidance of personal exposure, e.g. protective clothings (scrub typhus), handling of tick-infested dogs (Indian tick-typhus) and use of pasteurized/boiled milk (Q fever).
- Short-term weekly Doxycycline prophylaxis for up to 6 weeks may be recommended for travellers in setting of high-risk exposure.

10.18 MEASLES

Measles (Rubeola) is the *commonest vaccine-preventable illness*, characterized by fever, upper respiratory tract infection and generalized maculopapular rash with self-limiting course, but high morbidity and mortality. India aims to eliminate Measles and Rubella by 2023.

India contributes to highest number of measles cases in the world, though incidence has substantially declined in recent years. However, intermittent outbreaks are common, recent ones in Mumbai (2022) and Hyderabad (2023).

Epidemiology: Measles virus is an RNA virus of only one known serotype, present in nasopharyngeal secretions of infected clinical/sub-clinical human case. Infection is transmitted by *droplet infection*. Disease is highly contagious with secondary attack rate of as high as 80%, and *period of infectivity* extends from 4 days before to 5 days after the appearance of rash.

Maximum cases are seen in preschool children. Maternal antibodies in endemic regions protect infants till 4–6 months. Immunization or natural infection usually provides life-long immunity. Overcrowding and poor immunization coverage are two important predisposing factors for measles outbreaks in a community, more common in winter or spring season.

Pathogenesis: The sequence of events in pathogenesis of measles are: (a) *local viral multiplication* at the site of entry, i.e. nasopharynx, for short period, (b) *transient, asymptomatic primary viremia*, spreading virus to distant sites, specially lymphoid tissue, (c) *active multiplication* in lymphoid tissue for ~1 week, (d) *symptomatic secondary viremia* with development of clinical disease.

Essential pathology in measles is a generalized inflammatory reaction with perivascular infiltration, specially in skin (*rash*) and mucus membranes (*Koplik spots*) and *lymphoid hyperplasia*, specially in appendix with multinucleated giant cells (*Warthin-Finkeldey cells*). Other important changes include interstitial or Hecht giant cell pneumonia and perivascular demyelination (encephalomyelitis).

Clinical manifestations: While subclinical infections are common, typical case presents after an *incubation period* of ~10–12 days, with three stages:

a. ***Prodromal phase*** *(4–5 days)* with mild to moderate fever, upper respiratory illness with cough, coryza, etc. and conjunctivitis. Conjunctivitis is characterized by a transverse line of inflammation across the bulbar conjunctiva, sharply demarcated along the lid margins. *Koplik spots* are pathognomic lesions in this stage, seen as grayish-white sandy dots surrounded by slightly reddish areola, usually opposite the lower molars on oral mucosa. These spots are present from 2–3 days before to 24 hours after the appearance of rash, and herald the onset of skin rash **(Fig. 10.8)**.

b. ***Eruptive phase*** *(5–7 days):* Skin rashes appear on 4–5th day with transient rise of fever, starting as faint blanching macules, first along the hair-line behind the ears, face and neck. These rashes rapidly turn maculopapular and extend downward, involving whole body in next 2–3 days **(Fig. 10.8)**. Rashes may be associated with moderate cervical lymphadenopathy, constitutional symptoms, e.g. anorexia/malaise, GIT upsets, e.g. diarrhea, vomiting or abdominal pain due to mesenteric lymphadenopathy.

c. ***Convalescent phase*****:** Rashes disappear in the same sequence after 5–7 days, leaving behind a branny brown desquamation (post-measles staining) for next 10–15 days.

Fig. 10.8: Measles: (A) Active disease; (B) Post-measles staining.

TABLE 10.33: Complications of Measles

Early complications:
- *URTI* : Otitis media, laryngitis, tracheobronchitis
- *LRTI* : Pneumonia
- *GIT* : Enteritis (diarrhea), appendicitis*
- *CNS* : Encephalitis**, GBS, retrobulbar neuritis
- *lCVS* : Myocarditis
- *Hematological* : Purpura, DIC

Late complications
- Protein energy malnutrition
- Transient immunodeficiency (till 3 months)
- Re-activation of tubercular focus
- Bronchiectasis

Very late complications
- Subacute sclerosing pan-encephalitis (SSPE)

GBS: Guillain-Barré syndrome
*due to blocked lumen by lymphoid hyperplasia
**usually in second week, incidence ~ 1–2 per 1000 cases

Atypical presentations of measles include:
- ***Hemorrhagic (black) measles***, a life-threatening illness in immunocompromised children, characterized by high fever, confluent ecchymotic rashes, altered sensorium and bleeding diathesis.
- ***Modified measles*** with transient, few and faint macular rashes with minimal fever and constitutional symptoms, seen in immunized cases, young infants <9 months (due to maternal antibodies), *or* children who have received immunoglobulin prophylaxis in incubation period.

Complications: Although most cases recover spontaneously, complications are common in older or malnourished children, specially during convalescent phase **(Table 10.33)**.

Subacute sclerosing panencephalitis (SSPE) is a unique, rare and late complication of measles infection or vaccination, with an estimated incidence of ~ 8/million cases or <1/million doses of vaccine. Clinically presenting as a neurodegenerative disease after at least 4 years of primary infection, SSPE represents slow viral infection of CNS (see Ch.18.15).

Diagnosis of measles is mainly clinical, based on: (a) history of ongoing outbreak and unimmunized child, (b) typical rash after 4th–5th day of prodromal illness, (c) presence of *Koplik spots* for early diagnosis, and (d) *post-measles staining* for retrospective diagnosis.

Laboratory confirmation is rarely required and includes: (a) serological testing with >4-fold rise in IgM antibodies after 15 days, (b) viral culture on human embryonic or rhesus monkey kidney cells, (c) supportive evidences, e.g. leucopenia with relative lymphocytosis and presence of multi-nuclear giant cells or intracellular inclusion bodies in infected tissues after 5–10 days.

D/D include other causes of maculopapular rash (Ch 25.5), specially: (a) other exanthematous fevers **(Table 10.5)**, (b) allergic or drug rash, and (c) miliaria.

Treatment is mainly symptomatic with no specific antiviral therapy and includes: (a) maintenance of nutrition and hygiene, (b) antipyretics, (c) humidification to relieve cough, and (d) treatment of complications. *Two doses of vitamin A at 24 hours interval (PO 50,000 IU < 6 mo age, 1 lac IU in 6–12 mo infants and 2 lac IU in older children), are known to reduce the mortality and morbidity in measles by about 50%.*

Prevention involves avoidance of contact with an infected case along with *universal immunization* with two doses of a live-attenuated combination vaccine (MR) at the age of 9–12 months and 16–24 months, as per NIS. IAP recommends three doses of MMR at 9 mo, 15 mo and 4–6 years. (Ch 9.2.1).

Outbreak-control measures in measles include:
- *Supplementary immunization* rounds in outbreak areas, including *additional* dose to previously immunized children and the immunization in 6–9 months age group (zero dose).
- *Post-exposure prophylaxis* to reduce severity/duration of disease, only if received within 3–5 days of exposure. It is indicated only in high-risk household contacts, as follows:
  - Unimmunized infants (immunoglobulins* with vaccine)
  - Older unimmunized children without past history of disease (only vaccine)
  - Immunocompromised or pregnant contact (only immunoglobulin*)

  *(0.25 ml/kg of human immunoglobulin)
- *Isolation* of the case and susceptible contacts during infectivity period (7 days after exposure to 5 days after appearance of rash).

Measles-Rubella (MR) Elimination Plan in India by 2023 rests on four pillars: (a) 95% coverage with two doses of Measles-containing vaccine, (b) sensitive case-based MR surveillance, (c) rapid response to MR outbreaks, and (d) augmentation of the laboratory network for confirmation of diagnosis and virus typing.

Some other close mimics of Measles with Exanthematous fevers are also discussed as follows.

Rubella (German Measles) is a common RNA viral infection, with asymptomatic or mild self-limiting illness in children/adults. However, maternal infection in first trimester has serious consequences to fetus, e.g. fetal death or congenital rubella syndrome (Ch 12.15.3).

During 2017–2021, India adopted a National Strategic Plan for MR elimination (discussed below) and introduced rubella vaccination in National Immunization Schedule, replacing Measles vaccine with MR (Measles + Rubella) vaccine, apart from intensified surveillance. In 2019, India has adopted the goal of Measles and Rubella Elimination by 2023.

Epidemiology: Rubella is a RNA virus, present in nasopharynx, throat, and urine of infected person. Infection is usually acquired in school-age as droplet infection from a clinical or subclinical case, who is infective from 7 days before to 14 days after the rash.

As ~80% of Indian population is infected by late adolescence and conferred life-long immunity, 15–20% of pregnant mothers are still susceptible for rubella and consequent risk of CRS.

Pathologically, virus replicates in local epithelium and spreads to regional lymph nodes followed by viremia lasting for about 10–14 days. Fetal infection occurs transplacentally during the viremia, leading to extensive tissue damage, specially in brain, heart and auditory nerve.

Clinically, postnatal rubella is either asymptomatic or presents as mild, self-limiting viral illness, with: *(a) prodromal phase* (4–5 days) with mild catarrhal symptoms, and *(b) exanthematous phase* (2–3 days) with transient morbilliform or scarlatiniform rash and generalized lymphadenopathy, specially involving occipital and post-auricular nodes. Other features, e.g. *Forchheimer spots*—a rose-colored enanthem on soft palate and *arthralgia,* are common in adolescent girls.

Complications, other than congenital rubella syndrome after infection during pregnancy are extremely rare and include: (a) early complications, e.g. thrombocytopenia or Guillain-Barré syndrome, and (b) late complication, e.g. progressive rubella encephalitis.

Diagnosis is clinical, often missed due to nonspecific, transient illness. Laboratory confirmation requires elevated specific IgM antibodies *or* rising IgG titers on repeat testing.

Management: Rubella is self-limiting with no specific therapy, except symptomatic care.

Prevention of infection is specially important in prospective mothers and includes:

- ***Routine MR/MMR immunization*** at or after 15 months of age. (Ch 9.2.1). While single dose of rubella containing vaccine provides nearly 100% immunity, two doses of MR are given in India at 9 months and 15–18 months of age under National Immunization Programme. Indian Academy of Pediatrics recommends a third dose at 5–6 years. Vaccine may also be given at any age to unimmunized older children/adults, except during pregnancy. Conception should be strictly avoided for minimum three months after vaccination.
- ***Exposed pregnant and unimmunized women*** of reproductive age should be serologically screened immediately and after four weeks of exposure. Risk of congenital rubella syndrome is very low if mother is seropositive at the time of exposure. Seronegative mother, who turns seropositive after 4 weeks, carry maximum risk of congenital rubella syndrome and should be counseled accordingly. If abortion is not an option, immunoglobulin prophylaxis is indicated immediately after exposure, to reduce the risk of congenital rubella syndrome.

Erythema infectiosum *(fifth disease)* is the prototype illness of *Parvoviral B_{19} infection* in healthy children. Infection is acquired as droplet infection from a clinical or sub-clinical case, usually in *school-age.*

Clinically, infection is asymptomatic or presents as a mild febrile illness, *followed by* hallmark rash. Typical rash evolves in three stages:

a. Initial, transient facial flush (*slapped-cheek appearance*).
b. Discrete macular lesions over trunk and proximal extremities, *sparing palm and soles.*
c. Central clearing of macular lesions, with a lacy, reticular appearance.

Rash resolves spontaneously within 1–3 weeks, *without desquamation,* but may recur for a few weeks after sun exposure, heat, exercise and stress.

Diagnosis is mainly clinical, based on: (a) hallmark rash *without* fever and sick-appearance. Laboratory confirmation is not easily available, but includes: (a) elevated specific IgM titers, or (b) PCR testing. Virus cannot be isolated by culture.

Treatment is supportive and non-specific.

Other parvoviral illnesses: B_{19} is the only serotype of parvovirus, known to cause of human disease. It mainly targets erythroid cell line and other Parvovirus B_{19}-associated illnesses are:

- Transient aplastic crisis in hemolytic anemia, e.g. sickle cell disease,
- Chronic anemia or pancytopenia in immunocompromised host,
- A self-limiting arthropathy in female adolescents or adults, and
- Non-immune hydrops fetalis due to bone marrow depression and anemia in maternal infection.

Roseola infantum *(exanthem subitum)* is the prototype manifestation of a human herpesvirus type 6 or 7 (HHV 6/7) infection, characterized by a mild exanthematous febrile illness in infants and toddlers (d/d fifth disease in older children).

HHV 6/7 virus is present in saliva of infected humans and transmitted by close contact, e.g. kissing. Consequently, infection rate is highest in early infancy.

Clinically, it is characterized by:

- Sudden onset of high fever (>39–40°C) for 3–5 days that resolves with a crisis (suddenly). Typically, baby is apparently normal and active despite high fever. *Roseola is one of the commonest causes of febrile seizures.*

- Transient, discrete, maculopapular or rose-colored rash after 24–36 hours of defervescence, with centripetal distribution, most prominent on trunk and proximal extremities. Rash disappears rapidly within 1–3 days.

Complications are rare, except in immunocompromised host, who may develop aseptic meningitis or encephalitis.

Diagnosis is clinical, though laboratory confirmation is possible with—(a) elevated specific IgM titers, and (b) viral detection by culture or PCR amplification.

Treatment is supportive and non-specific. Ganciclovir and Foscarnet may be used for severe CNS disease in immunocompromised host.

Other HHV 6/7 illnesses, presumably associated with life-long persistence of these infections are:

- Blood disorders, e.g. hemophagocytic syndrome, histiocytosis and immune thrombocytopenia.
- Intussusception.
- Pityriasis rosea.
- Multiple sclerosis in adults.
- It is also considered as a co-factor in progression of HIV/AIDS infection.

10.19 CHICKENPOX

Varicella-zoster virus (VCZ) infection presents either as a primary infection, i.e. *chickenpox* in reviously nonimmune child or as re-activation of earlier latent infection, i.e. *herpes zoster (shingles)*. Chickenpox is a common and highly contagious exanthematous illness in children, usually seen as outbreaks.

Epidemiology: VCZ is a neurotropic human herpes virus, present in respiratory secretions or skin vesicles of a clinical case of chickenpox or herpes zoster (1–2 days before to 5–7 days after the rash).

Infection, transmitted via direct contact or as droplet infection, is highly contagious with secondary attack rate of 80–90% in household contacts and 30–35% in schoolmates. Transplacental fetal infection is possible in pregnant mothers with VCZ infection.

Chickenpox is most common in 5–9 year age group, though no age is immune, *including newborns*. Although infection confers life-long immunity, reactivation of silent infection (herpes-zoster) may occur after many years in ~ 10%, specially in immunocompromised states. Chickenpox outbreaks are more common during January to May months.

Pathogenesis: After primary infection, virus replicates locally in respiratory tract with intermittent subclinical viremia. After incubation period of 10–21 days, secondary or major viremia develops with onset of clinical disease. Gradual development of immune response limits the infection with clinical recovery within 5–7 days. However, VCZ virus invariably persists in body as a latent infection of *sensory ganglion* cells, which may be re-activated later to produce herpes zoster.

Fig. 10.9: Chickenpox.

Pathology: Typical skin vesicles containing *classic giant cells with Cowdry type A eosionophilic intranuclear inclusion bodies* are pathological hallmark of chickenpox. Similar cells may also be seen in other tissues, e.g. esophagus, pancreas, liver, lungs and brain.

Clinical presentation is variable, with milder disease in younger children. A typical case present after *incubation period* of 10–21 days, with:

- ***Short prodromal illness*** (1–2 days) with mild/moderate fever and constitutional symptoms like malaise, anorexia, etc.
- ***Exanthematous phase,*** characterized by typical *pleomorphic* rash, from 2nd day of fever. Rashes appear in crops as intensely pruritic erythematous macules, which evolve rapidly into clear fluid-filled vesicles and crust within 24–48 hours **(Fig. 10.9)**. Lesions are typically *centripetal in distribution,* mainly seen on trunk and back. New rashes continue to erupt for next 3–4 days, leading to *pleomorphism*, i.e. simultaneous presence of rashes in different stages of evolution as macules, papules, vesicles and scabs. Mucosal lesions, i.e. *enanthem,* may be present on oropharyngeal mucosa, airways, conjunctiva and vagina, as ulcerative lesions.
- ***Convalescent phase***, when scabs gradually fall-off in 7–14 days, leaving behind hypopigmented scars for 4–8 weeks.

Atypical variants of chickenpox include:

- ***Modified varicella-like illness (MVLI),*** seen in < 5% vaccinees, presents as mild papulovesicular eruptions after 1–3 weeks, lasting for few days.
- ***Breakthrough varicella*** is defined as a clinical disease after 42 days of immunization (d/d MVLI, within 1–3 weeks), usually seen in 1–4% vaccinees within 2–5 years of vaccination. It is more common in children vaccinated <15 months of age with a single dose and represents inadequate immune response with waning of the immunity over time. Two doses reduce the risk of breakthrough varicella by 3.3 fold.

- ***Hemorrhagic chickenpox*** in immunocompromised host, presenting with severe, hemorrhagic skin lesions, visceral complications and longer course.
- ***Congenital varicella*** *syndrome* may develop in 1–2% cases if mother is infected in before 20 weeks of gestation, characterized by limb hypoplasia, skin scarring, microcephaly and eye problems, e.g. cataracts and microphthalmia.
- ***Neonatal varicella*** is a life-threatening complication following primary maternal varicella infection 5 days prior to delivery and 2 days afterward, seen in 20–30% cases. Transplacental fetal infection may present with severe cutaneous and visceral lesions in first two weeks, with pneumonitis and fatal disseminated disease in 30% cases. Varicella zoster immunoglobulin (VZIG) at birth may reduce the severity of disease. Symptomatic newborns must be intensively treated with IV Acyclovir (10 mg/kg 8-hrly)
- ***Herpes zoster*** rarely presents in childhood, with typical unilateral *dermatomal distribution of grouped vesicular lesions,* which heal spontaneously within 1–2 weeks. Recurrent or multi-dermatomal herpes zoster indicates immunodeficiency state, e.g. HIV.

Complications are extremely rare in younger children, usually seen in older children, adults or immunocompromised host **(Table 10.34)**.

Diagnosis is mainly clinical, although laboratory confirmation is possible using vesicular fluid sample for: (a) virus detection by PCR or culture, (b) serological tests, e.g. immunofluorescence or ELISA, and (c) demonstration of multinucleated giant cells on *Tzanck smear.*

D/D includes other causes of vesicular lesions, e.g. (a) impetigo, (b) herpes simplex, (c) enteroviral rash, (d) drug-rash (e) insect-bites, etc. (Ch 25.6).

Treatment is symptomatic with maintenance of personal hygiene, mild antipyretic, e.g. paracetamol and topical anti-pruritic agents like zinc-calamine lotion. Aspirin is contraindicated in chickenpox due to high-riskof Reye-like syndrome.

Antiviral therapy is indicated to reduce the severity/duration of illness in high-risk cases, i.e. (a) immunocompromised states, (b) older cases >12 years, (c) pre-existing skin or pulmonary disorders, and (d) complications, e.g. encephalopathy, pneumonia and bleeding diathesis. It should be started within 24 hours of appearance of rash, using PO/IV Acyclovir (20 mg/kg/dose QID) for 5–7 days or till no new lesions appear for 48 hours.

Herpes zoster may also be treated with PO acyclovir, though IV therapy is necessary in immunocompromised cases with risk of disseminated disease. Other alternatives include famciclovir or valacyclovir, though rarely used in children.

Prevention of chickenpox includes:

- *Active immunization:* While not included in National Immunization Schedule, IAP recommends varicella vaccine to all children with two doses-first at 15–18 months of age and second after 3–6 months. Catch-up immunization is advised till 18 years with two doses at 8–12 weeks interval.

  Varicella vaccine is specially recommended in high-risk cases, e.g. close contacts of index case (within 3 days), institutionalized children or immunocompromised host (Ch 9.2.2)
- *Passive prophylaxis* with VZIG, i.e. specific varicella-zoster immunoglobulin (IM one vial/10 kg body weight) is indicated in: (a) immunocompromised or close household contacts, (b) pregnant women and (c) newborns born to mothers who develop varicella within 5 days before or 2 days after the delivery. It is effective only if given within 48–96 hours of exposure.
- *Isolation* is difficult but the child should not be sent to school during infectivity period. A case is contagious from 24–48 hours before the rash to 5–7 days after rash, till all vesicles have crusted.

TABLE 10.34: Complications of chickenpox

• *Skin*	:	Secondary bacterial infection of rash
• *Resp*	:	Interstitial pneumonia
• *Blood*	:	Thrombocytopenia, *P. fulminans*, DIC
• *CNS*	:	Cerebellar ataxia, encephalopathy, GBS
• *Renal*	:	HUS, acute nephritis, nephrotic syndrome
• *GIT*	:	Transient hepatitis or Reye-like syndrome*
• *Cardiac*	:	Pericarditis, myocarditis
• *Others*	:	Arthritis, pancreatitis, orchitis

HUS: Hemolytic-uremic syndrome, **GBS:** Guillain-Barré syndrome
*associated with use of aspirin in these cases

10.20 MUMPS

Mumps is a common vaccine preventable illness, characterized by acute, self-limiting, painful enlargement of parotids and other salivary glands, rarely associated with systemic complications.

Epidemiology: Mumps is a RNA virus (Paramyxovirus) of only one known serotype, with a clinical or subclinical infected human case as reservoir. A case is usually contagious from 24 hours before the swelling to 3 days after its disappearance and infection spreads by exchange of highly-infective saliva *via* direct contact, air-borne droplets or contaminated fomites.

It is most common in 5–9 year age group, though no age is immune except infants <6 months due to presence of maternal antibodies. Lifelong immunity develops after clinical/subclinical attack or immunization. Outbreaks are common in late winter or spring season.

Pathogenesis: After infection, virus multiplies in respiratory mucosa during incubation period, followed by viremia and localization of virus in *salivary glands*-the

Fig. 10.10: **Mumps: (A) Unilateral parotitis; (B) Bilateral parotitis**

commonest site of clinical disease, and other tissues. About 40% of infections are subclinical.

Clinical manifestations: After an *incubation period* of ~17–18 days, mumps presents with:

- *A brief prodromal phase (1–2 days)*, which is less prominent in younger children and includes moderate fever, malaise, pre-auricular pain and difficulty in chewing.
- *Shiny, tender, parotid swelling after 24–48 hours*, which gradually increases in size for next 2–3 days. Parotid enlargement is bilateral in 75% cases, though one side usually involve earlier than other side. Severity of parotid enlargement may vary from: (a) fullness of pre-auricular region, (b) lifting of ear pinna, (c) obvious parotid swelling, and (d) bull-neck appearance in bilateral parotitis **(Fig. 10.10)**. Opening of the *Stensen's duct*, opposite upper second molar, is red and swollen. Submandibular and submaxillary glands may be mildly enlarged.
- *Convalescence* begins after 3–4 days of swelling with complete recovery within 7–10 days.

Complications are rare (<1%), most important being aseptic meningitis, meningoencephalitis, orchitis and pancreatitis **(Table 10.35)**.

Aseptic meningitis is the commonest complication of mumps in childhood in 8–10% cases, though ~90% of them are asymptomatic, except CSF pleocytosis. Symptomatic cases present with headache, photophobia and neck stiffness within few days of parotid swelling usually to recover spontaneously within a week.

Meningoencephalitis, is relatively less common and may develop either in acute phase due to direct viral invasion or after 2–3 weeks of disappearance of swelling due to post-infectious demyelination.

Orchitis is more common in adolescents or adults (~25%), presenting as sudden testicular pain and swelling during 2nd weeks of parotid swelling, which improves spontaneously in 3–4 days. Testicular atrophy may occur in ~30% cases, though sterility is uncommon except in bilateral orchitis.

Pancreatitis presents in ~4% cases, with acute abdominal pain during 2nd week, though sub-clinical pancreatitis with >3–4 fold rise in serum amylase level is more common. Mumps virus has been proposed to infect pancreatic beta cells to trigger onset of juvenile diabetes mellitus.

TABLE 10.35: Complication of Mumps

Common
- CNS : Meningoencephalitis, aseptic meningitis
- Gonadal : Orchitis, epididymitis and oopheritis
- Pancreatitis

Uncommon
- CVS : Myocarditis, endocardial fibroelastosis
- CNS : Transverse myelitis, sensory-neural deafness
- Ocular : Dacroadenitis, uveokeratitis
- Others : Arthritis, nephritis, thyroiditis

Antenatal infection *(mumps embryopathy)*
- Abortion, stillbirth, low birth weight
- Endocardial fibroelastosis
- Aqueductal stenosis and hydrocephalus

Antenatal mumps infection may be associated with abortion, stillbirth or *mump's embryopathy*-characterized by intrauterine growth retardation, endocardial fibroelastosis and hydrocephalus.

Diagnosis is usually clinical, but may be confirmed by IgM-ELISA test, or viral cultures from saliva, CSF and urine. Serum amylase levels are raised in proportion to the size of swelling and normalize within 2–3 weeks.

D/D of mumps include *other causes of parotitis* like: (a) acute suppurative parotitis, usually due to staphylococci, (b) salivary calculus, (c) parotitis due to other viruses, e.g. HIV, coxsackievirus etc., (d) recurrent allergic parotitis; or *other causes of neck swelling*, e.g. (e) pre-auricular lymphadinitis.

Treatment: There is no specific antiviral therapy and treatment is entirely symptomatic including antipyretics, e.g. paracetamol, bed rest, maintenance of oral hygiene with warm-saline oral washes and soft-liquid diet. Cases should avoid contact with others during infectivity period (~10 days after onset of swelling) to prevent the spread.

Prevention: Routine immunization with single-dose, live-attenuated, combination MMR vaccine at the age of 15–18 months has >97% protective value. MMR is not yet included in National Immunization Schedule due to lack of sufficient data on disease and severity burden of mumps. However, IAP recommends three doses of MMR at 9 months, 15–18 months and 5–6 years to all children, the last dose to prevent outbreaks in older age groups as antibody titers tend to decline over time. Only two doses of MMR, given 8 weeks apart, are enough if the first dose is given after 12 months of age.

10.21 ACUTE POLIOMYELITIS

After successful eradication of smallpox in 1978, poliomyelitis is the second infectious disease on the

verge of eradication. Sporadic cases of poliomyelitis due to wild poliovirus are being reported only from two countries—Pakistan and Afghanistan. No such case has been reported from India since 13th January 2011 and WHO has declared India polio-free w.e.f. 27th March 2014.

Epidemiology: Polioviruses are the small RNA enteroviruses with three serotypes—types 1, 2 and 3.

All global cases presently are due to type 1, as wild type 2 and 3 virus have been eradicated in 1999 and 2020 respectively.

Reservoir of infection is a symptomatic or carrier case, excreting virus in stools. As the virus cannot survive outside human body for >48 hours, presence of large number of non-immunized hosts is essential for propagation of infection.

Infection is mainly transmitted *feco-orally* due to contaminated water supply, rarely by contaminated fingers or as droplet infection in close contacts.

Poliomyelitis largely affects young children <5 years. Infants <3 months are relatively protected by transplacental immunity.

Maximum cases occur in late summer or rainy season. Poor sanitation and inadequate immunization coverage are important determinants of polio outbreaks.

Pathogenesis: After ingestion, virus replicates in intestines and regional lymph nodes for few days, followed by transient *primary viremia,* during which the reticuloendothelial system is infected. Subsequently, sustained viral replication in reticuloendothelial system leads to *secondary viremia* and CNS involvement. Virus traverses to the CNS, either along the nerve pathways or through the blood stream. *Local IgA-mediated intestinal immunity* is the first line of defence against polio virus invasion, while systemic immunity may neutralize the virus before CNS involvement.

While ~90% of infections are subclinical, some provoking factors increase the risk of symptomatic disease, by increasing spinal vascularity and risk of viral invasion and include: (a) intramuscular injections, (b) surgery, (c) muscle trauma and (d) strenuous physical exercise.

CNS injury is caused by direct viral invasion as well as immunological mechanisms and selectively affects the *anterior horn cells* of spinal cord, cranial nerve nuclei and vital centers in the brain stem and motor cortex, *sparing* rest of the cerebral cortex and spinal white matter.

Clinically, symptomatic cases present after an incubation period of 7–14 days, with:

- ***Abortive poliomyelitis*** (4–8%), as self-limiting non-specific febrile illness,
- ***Non-paralytic poliomyelitis*** (1–2%), which may or may not progress to paralytic stage, with intense headache, nausea/vomiting and soreness/stiffness of neck and back muscles. *Nuchal-spinal rigidity* is the clinical hallmark of these cases,
- ***Paralytic poliomyelitis*** (<1%) presents as acute *spinal, bulbar or spino-bulbar* paralysis.

Spinal poliomyelitis is characterized by *acute flaccid paralysis* of different group of muscles involving neck, trunk or limb, with/without diaphragmatic involvement. Paralysis is typically a*symmetric and patchy* with variable severity. Involves muscles are quite tender urinary retention and constipation is common (20%) due to autonomic involvement. New areas of weakness may appear till next 3–7 days, followed by gradual recovery to some extent. Involvement of diaphragmatic/intercostal muscles indicates impending respiratory failure.

Bulbar poliomyelitis due to involvement of cranial nerve nuclei and/or respiratory center in the brain stem may also develop in some cases, presenting with feeding and breathing difficulties. Isolated encephalitic poliomyelitis is extremely rare.

Diagnosis: *Each case of acute flaccid paralysis (AFP) is considered as potential poliomyelitis for surveillance purpose, however unlikely it may be, and needs to be reported (discussed later).*

Clinical diagnosis rests on—(a) epidemiological history, (b) unimmunized child, and (c) acute onset of asymmetrical/patchy flaccid paralysis with pain/tenderness of involved muscles.

Laboratory diagnosis depends on *viral culture from stools,* which should be collected (~8 gm or thumb size) and transported to designated laboratory in ice pack (reverse cold-chain) as early as possible, under AFP surveillance program.

D/D of acute paralytic poliomyelitis includes: (a) vaccine associated illness, e.g. VAPP or VDPV, (b) other causes of AFP **(Table 10.36)**, or (c) *pseudoparalysis* due to pain, e.g. in scurvy, osteomyelitis, trauma, etc.

Possibility of vaccine related disease (VAPP/VDPV) should be considered in any case of AFP with history of: (a) OPV vaccination in preceding 30 days, (b) contact with recently immunized child in preceding 60 days, or (c) mass immunization program, i.e. *pulse polio* in the community, in preceding 60 days.

Management is non-specific, aims to: (a) provide supportive care during acute phase, (b) treat complications, e.g. respiratory failure, and (c) minimize residual functional loss with physiotherapy, orthotic corrections and occupational rehabilitation. All suspected cases should be hospitalized and notified to public health authorities

Prevention largely depends on adequate immunization, using an oral live-attenuated *Sabin* vaccine or a parenteral, inactivated *Salk* vaccine (Ch 9.2.1).

Polio Eradication in India

In May 1988, WHO launched a *global polio eradication initiative* and wild poliovirus 2 and 3 have been

TABLE 10.36: D/D common causes of acute flaccid paralysis (AFP)

	Poliomyelitis	*Guillain-Barré syndrome*	*Transverse myelitis*	*Traumatic neuritis*
Common age	< 5 years	Any	> 5 years	Any
Preceding events	Prodromal fever	Viral infection*	Viral infection	Trauma
Paralysis characteristics				
Symmetry	Asymmetrical	Symmetrical	Symmetrical	Asymmetrical
Progression	Patchy	Ascending	Changing signs**	Nil
Topology	Proximal	Distal	Proximal	Monoparesis
Associated involvement				
Sensory	Absent	Usual	+++ (identifiable level)	+/- Parasthesia
Cranial nerves	Bulbar only	Common	Absent	Absent
Bladder	Transient	+/–	+++	Absent
CSF findings	Pleocytosis	↑ proteins***	Non-specific	Normal
Motor recovery	Poor	Excellent	+/–	+/–

*2–3 weeks before. **Flaccidity rarely lasts for > 72 hours, changes to spasticity. ***with near normal cell count, i.e. albumino-cytological dissociation

eradicated in 1999 and 2020 respectively. However, sporadic cases of WPV1 are still being reported from two countries – Pakistan and Afghanistan.

Despite being polio-free since 2014, eradication measures need to be continue here till disease is eradicated globally due to potential risk of spread through travellers from endemic countries.

Strategies for polio eradication in India included: (a) routine immunization, (b) supplementary immunizations, e.g. pulse polio immunization, (c) AFP surveillance, (d) environmental surveillance, and (e) outbreak control measures.

Pulse polio immunization (PPI) is a mass immunization campaign to supplement routine immunization and to facilitate development of herd immunity, conducted annually and simultaneously (pulse) throughout the country on pre-fixed dates (national immunization day/s or NIDs).

Principle: Since the vaccine-virus is excreted in stools for 4–6 weeks, simultaneous OPV administration to large population leads to extensive dissemination of vaccine virus in community, which competes with wild-virus for gut uptake. As wild-virus cannot survive in external involvement for long, it is expected to be flushed-out from community, replaced by non-virulent vaccine virus.

Target population for PPI is all children <5 years of age (including newborns), irrespective of previous immunization status. OPV doses during PPI are additional and should not replace regular immunization dose. There are no contraindications for PPI, even if routine dose was given a few days back.

Immunization days: First country-wide pulse polio campaign was launched on 9th December, 1995 and presently one polio immunization day is held nationally (NID) and with 1–2 additional state immunization days (SIDs) in high risk-states. These days are decided in advance using a Sunday and during winter season, as the wild-virus circulation is least common in these months and consequently, vaccine uptake is better. All infants are administered 2 drops of oral polio dose on this day at designated community centers or by door-to-door outreach for missed cases during next one week.

Acute flaccid paralysis (AFP) surveillance is an essential component of global polio eradiation initiative, "*to detect all cases of wild polio virus disease and eliminate remaining foci of polio transmission*", undertaken in India since 1997 as National Polio Surveillance Project (NPSP). Surveillance is carried out for all cases of AFP and not only for polio.

What is AFP? AFP is defined as "*any illness presenting with acute onset of flaccid paralysis in a child <15 years, for which no obvious cause such as trauma or electrolyte imbalance is found or a person of any age, with clinical suspicion of polio*". Generally, AFP of < 4 weeks is considered as acute.

Why all cases of AFP should be investigated? Since it is often difficult to exclude the diagnosis of poliomyelitis in a suspected case at the time of presentation, it is essential to investigate each case of AFP, to ensure that all cases are detected, reported and investigated and no case is missed out.

Components of AFP surveillance include, regular reporting system, investigation of suspected case and outbreak-control measures after suspected case report.

- ***Reporting:*** All *field-reporting units, e.g.* district health centers or pediatric units of major hospitals collect and send weekly reports of suspected case/s. If no case is seen during reporting week, the report has to be sent as *'nil or zero report'*
- ***Investigation of suspected AFP case*** includes: (a) *immediate reporting* to the designated person, (b) detailed data collection and *line-listing of all* reported

cases with a unique EPID number, to prevent duplication of reports, (c) *collection of stool cultures* for virus isolation, as specified earlier.

- ***Outbreak-containment measures*** are activated for every reported case of AFP with: (a) immunization of under-5 children in vicinity of suspected case, (b) intensified *collection of random stool and water/sewage samples* to detect the presence of wild-virus, and (c) *active case surveillance by door-to-door survey.*

Classification of an AFP case: All cases of reported AFP are classified after detailed epidemiological and viral studies as polio or non-polio cases.

An AFP case is confirmed as *poliomyelitis only* if: (a) wild polio virus isolated from stool sample, or in absence of adequate stool sample, (b) cases continues to have residual weakness after 60 days of onset *or* 60 days-follow-up not available due to death or absence *and* expert review concludes that these cases could not be discarded as *non-polio* based on available data.

10.22 ENTEROVIRAL INFECTIONS (NON-POLIO)

Enteroviral infections are caused by a large group of RNA viruses, which typically inhibit the intestinal tract. These infections include 3 distinct subgroups—(a) polioviruses, (b) echoviruses and (c) coxsackieviruses A and B, each with various serotypes.

Non-polio-enteroviral infections are usually caused by echo 4, 6, 9, 11, 30, coxsackie-A9, 16 and coxsackie B 2–5 viruses, most prevalent being echovirus 9.

Epidemiology: These viruses are widely present in soil and sewage water, sourced from human reservoirs and infection spreads via fecooral route or as droplet infection. Outbreaks are common in summer season, specially in overcrowded settings, e.g. slums, day-care centers, etc.

Clinical spectrum of these infections varies from asymptomatic infection to non-specific febrile illness to serious systemic illnesses **(Table 10.37)**.

Diagnosis of enteroviral illness should be considered in any febrile illness with rash or mucosal lesions, specially during outbreaks. Confirmation requires—(a) *viral cultures* from rectum swab or stools, throat and other infected sites, e.g. CSF, followed by serotyping, (b) PCR test for early diagnosis, and (c) serological studies, i.e. neutralizing antibody titers, for retrospective diagnosis.

Treatment is non-specific and supportive. *steroids are contraindicated*. No vaccine is available, though passive prophylaxis with human immunoglobulins may be useful during nursery outbreaks with virulent strains.

Some common and important enteroviral infections in Indian children are as follows:

Hand-foot-mouth disease *(HFMD)* is the commonest enteroviral illness in infants and toddlers, usually seen as localized outbreaks in winter season.

Etiologically, most cases are caused by *coxsackie A16 or Enterovirus A71,* though other serotypes have also been implicated.

Clinically, HFMD present with acute onset of: (a) oropharyngeal ulcers, and (b) tender vesicular lesions over dorsum of hands/feet, bony prominences like knee/elbow, palm/soles and buttocks, after incubation period of 3–7 days **(Fig. 10.11)**. Presence of lesion over palm and soles is characteristic in HFMD. Fever is rarely prominent and does not last for >24–48 hours. Patient is most infectious during the first week.

Most cases recover within 7–10 days and complications are extremely rare, though interstitial pneumonia, myocarditis or aseptic meningitis/encephalitis have been reported in few cases.

Diagnosis is clinical, though virus may be isolated from oropharynx and stools for 4–6 weeks.

Management is supportive with assurance about self-limiting nature of disease, analgesics and topical soothing agents, e.g. zinc-calamine lotion over skin or anesthetic mouth paints. Adequate nutrition and hydration must be ensured as children avoid oral intake due to ulcers.

Herpangina, is a self-limiting illness due to *Echovirus 9*, characterized by: (a) sudden onset of fever, headache and vomiting, (b) oropharyngeal discrete vesicles/ulcers with erythematous base, (c) morbilliform or petechial

TABLE 10.37: Clinical spectrum of enteroviral infections

• Asymptomatic infection (~50%)
• Non-specific febrile illness
• *Exanthemous illness:* Herpangina, HFMD
• Acute hemorrhagic conjunctivitis
• *Respiratory:* URTI, bronchitis, pleurodynia, ? asthma
• *GIT:* Vomiting, diarrhea, Abd. pain (d/d surgical abd.)
• *CNS:* Aseptic meningitis, encephalitis, GBS, C. ataxia
• *Others:* Myositis, arthritis, myocarditis, orchitis*
• *Neonatal infections:* Sepsis-like illness, myocarditis

*Enteroviruses are 2nd common cause of orchitis after mumps.
HFMD: Hand-foot-mouth disease, **GBS:** Guillain-Barré syndrome

Fig. 10.11: Hand-foot-mouth disease: (A) Skin lesions; (B) Oral ulcers.

rash in some cases. Most cases recover spontaneously in 3–5 days, though some may develop aseptic meningitis.

Acute hemorrhagic conjunctivitis, due to echovirus 70, presents with epidemics of viral conjunctivitis during post-monsoon season, characterized by-red-eye, conjunctival follicles and sub-conjunctival hemorrhages. Conjunctival discharge is highly contagious and epidemic spreads via hand-fomite-eye route. Recovery is spontaneous in 3–5 days, though rarely complicated by keratitis/corneal ulcers and polyradiculoneuropathy.

Pleurodynia (Bornholm disease), due to various serotypes of coxsackie B, is a self-limiting epidemic illness, presenting as acute high fever and severe spasmodic chest pain that is aggravated on deep inspiration. Pleural rub is common but effusions are rare. Most cases recover spontaneously in 1–3 days, though some may develop aseptic meningitis or pericarditis/myocarditis.

10.23 DENGUE

Dengue, the commonest *Arthropod-borne (ARBO) viral* illness, is a major public health problem in India with many outbreaks in recent years, usually in urban population.

Disease presents with many clinical variants-asymptomatic illness, classical dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock-like syndrome (DSS).

Epidemiology: Dengue fever is caused by one or more of the four serotypes (DENV 1–4), though severe disease, e.g. DHF/DSS is more common with serotype 2.

An infected case is the usual reservoir of infection, which is mainly transmitted by a mosquito '*Aedes aegypti*'. This mosquito has typical daytime biting habit and breeds on stored water in houses. Rain water collected on terrace junks, is a major cause of increased vector density and focal outbreaks in urban slums at the end of rainy season. As the vector cannot fly for long distance, movement of infected persons is the major cause of distant transmission in dengue fever.

Mosquito is infected after feeding on a patient in viremic stage (1–5 day after onset of illness) and becomes infective after an extrinsic incubation period of 8–10 days. Vector, once infected, remains infective for life.

Etiopathogenesis is complex and still evolving.

- *First infection* in previously unexposed person leads to transient viremia after an incubation period of 5–7 days, which is either asymptomatic or presents with nonspecific febrile illness or classical dengue fever. At the end of viremia, these patients develop—(a) *homo-type neutralizing antibodies* to provide life-long immunity against same serotype; and (b) *hetero-type nonneutralizing antibodies,* which unfavourably alter the course of second infection with different serotype.
- *Second infection* with same serotype is asymptomatic but by different serotype may present with severe DHF/DSS due to pre-existing non-neutralizing antibodies, immune complex formation and intense inflammatory response.

Pathology of DHS/DSS is mediated by activation of complement system and release of many inflammatory mediators, like cytokines, leading to:

- *Vasculopathy*, i.e. increased permeability with extravascular shift of fluids, leading to shock and hemoconcentration,
- *Coagulopathy,* due to activation of clotting/fibrinolytic mechanisms with DIC-like bleeding manifestations, and
- *Multi-organ dysfunction* due to above changes.

Clinical spectrum of dengue spans from asymptomatic infection to severe life-threatening disease, and includes:

Undifferentiated dengue fever, more common in younger children, presents as non-specific febrile illness, usually associated with—(a) generalized *erythematous flush* over body with suffused face **(Fig. 10.12)**, and (b) *absence of catarrh,* despite nasopharyngeal and ocular congestion. Signs of bleeding or capillary leakage are absent.

Classic dengue fever usually presents as biphasic illness as follows:

- ***Febrile phase** with*—(a) sudden onset of continuous high fever, (b) severe headache, myalgia, arthralgia and *retro-orbital* pain, (c) generalized macular rash/flush after 48–72 hours, usually sparing palms and soles, (d) disproportionate bradycardia, and (e) conjunctival congestion, rhinopharyngitis and nausea/vomiting. Fever usually comes down by lysis and profuse sweating after 3–5 days.
- ***Critical (leakage) phase*** begins after 3–5 days with development of increased capillary permeability and signs of plasma leakage from intravascular to extravascular compartment, e.g. hypotension, pleural

Fig. 10.12: Dengue: (A) Suffused or flushed face; (B) Macular rash.

effusion and rising hematocrit. Many warning signs during this phase **(Table 10.38)**, may herald the onset of dengue hemorrhagic fever (DHF) and/or dengue shock syndrome (DSS), discussed later. This phase usually lasts for 36–48 hours.

- ***Convalescent (recovery) phase*** begins after 6–7 days of fever with clinical improvement due to control of capillary leakage and return of the leaked plasma back into intravascular compartment. Patient may develop pulmonary edema due to fluid overload, if the overzealous fluid replacement continues.

Dengue hemorrhagic fever or shock-like syndrome (DHF/DSS), is a serious, life-threatening manifestation, with first phase similar to classical dengue fever. However, these cases deteriorate rapidly on 2nd–5th day, with bleeding tendency, thrombocytopenia, evidence of plasma leakage with or without circulatory shock. Severity of DHF/DSS may be classified into four grades, according to two clinical hallmarks—*bleeding* and *shock* **(Table 10.39)**. After 24–36 hours of crisis, recovery begins in adequately treated cases, though mortality is high (40–50%) in others.

Expanded dengue syndrome denotes multiple organ involvement in these cases, e.g. encephalopathy, hepatitis, renal failure, myocarditis or ARDS, more common in adults or those with co-morbidities.

National guidelines for clinical management of dengue fever (2023) classify dengue fever as asymptomatic and symptomatic, later further sub-classified as *mild* (without warning signs), *moderate* (with warning signs) or *severe* (with shock, bleeding or organ involvement) dengue based on various indicators **(Fig. 10.13)**.

Diagnosis rests on clinical suspicion, with laboratory tests to confirm the presence of virus, antigen or antibodies. Timing of the tests is important, dependent on the course of disease. Commonly used diagnostic tests include:

- ***NS1 antigen test:*** Non-structural protein (NS1) antigen is present in the serum during first 5–7 days of fever and its detection by an ELISA-based test helps in early diagnosis of dengue. However, the antigen disappears after 4–5 days and the test becomes negative. While rapid card tests for qualitative detection of NS1 using immunochromatography are also available, results are unreliable as compared to ELISA test, due to poor sensitivity.
- ***Anti-dengue IgM antibody test:*** These antibodies are detectable usually by day 5 of the illness and persist for ~ 60 days. Detection of these antibodies by ELISA or rapid tests help in diagnosis of disease after 5 days. However, rapid tests are not recommended due to high rate of false-negativity.
- ***Polymerase chain reaction (PCR):*** Molecular diagnosis based on detection of viral nucleic acid by RT-PCR is confirmatory in acute phase but the test may be negative after first week of illness.

Viral isolation or IgG antibody tests are of limited value in the diagnosis of acute disease.

Supporting investigations include hematocrit, platelet count and relevant tests for organ dysfunction, which need to be repeated frequently to monitor the progression of disease. Hematocrit and platelet count should be monitored at least every 24 hours for early detection of warning signs, i.e. hemoconcentration (due to capillary leak) and thrombocytopenia, though more frequently in severe dengue.

Table 10.40 presents current WHO/NVBDCP case definitions for dengue fever and related conditions.

D/D of dengue includes other causes of viral and non-viral hemorrhagic fevers (Ch. 10.1.14). Dengue-like illnesses have also been reported in India from other arboviruses, e.g. chikungunya virus and West Nile virus.

Management is essentially symptomatic and supportive, depending on the severity of disease, as follows:

DF without warning signs need not be hospitalized and may be managed at home with bed rest, antipyretics, adequate oral hydration and monitoring for the warning signs. NSAIDs, e.g. aspirin or Ibuprofen should be avoided due to risk of gastritis, platelet dysfunction and bleeding. ORS or fruit juices are preferable to plain water for rehydration to replenish fluid and electrolyte losses due to excessive sweating or vomiting. However, parents should be counselled about the need to observe for warning signs, which require urgent medical attention.

DF with warning signs: Immediate hospitalization is recommended to all cases with warning signs for close

TABLE 10.38: Warning symptoms and signs in dengue fever

- Persistent vomiting
- Abdominal pain or tenderness
- Lethargy, restlessness or irritability
- Hepatomegaly (>2 cm)
- Clinical fluid accumulation (ascites, pleural effusion)
- Bleeding manifestations, usually mucosal bleeds
- Rising hematocrit with concurrent drop in platelet count

TABLE 10.39: Severity grading of DHF/DSS

I	Dengue fever + positive tourniquet test and evidence of plasma leakage
II	*As above* + spontaneous bleeding and abdominal pain
III	*As above* + evidence of circulatory failure
IV	Profound shock with undetectable BP/pulse
Plus	Thrombocytopenia <100000 cells/mm^3, *and* more than 20% rise in hematocrit.

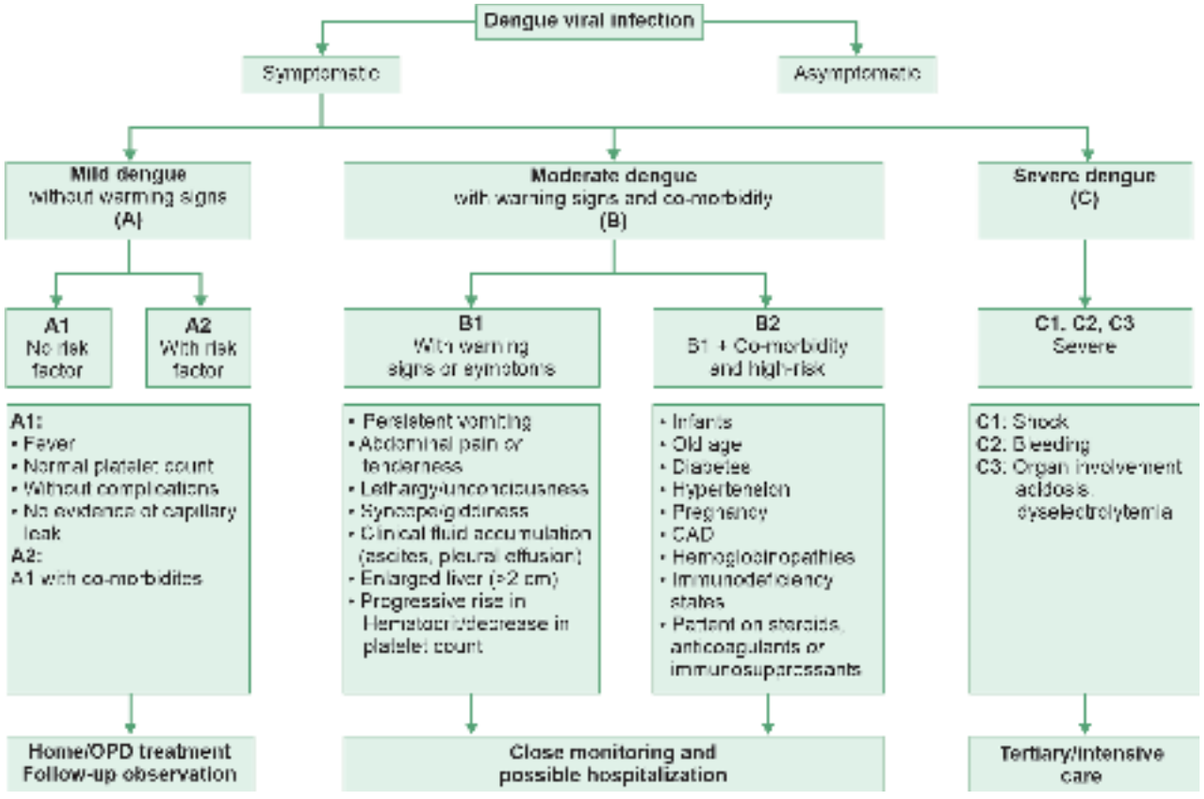

Fig. 10.13: Clinical case classification of Dengue: National Guidelines 2023.

TABLE 10.40: Case definitions for dengue fever/DHS/DSS

Probable dengue fever *(any one of following)*
- Acute febrile Illness (2–7 days) with *(any 2 of following)* Headache, retro-orbital pain, rash, myalgia, arthalgia, bleeding, thrombocytopenia or leucopenia, warning signs or symptoms
- Positive NS1/IgM test (non-ELISA based)

Confirmed dengue fever *(Clinically compatible, with any one of following)*
- Positive NS1 test by ELISA
- Positive anti-dengue IgM antibodies by ELISA
- Positive dengue PCR test
- Viral isolation from serum, plasma or leukocytes
- >4 fold rise in IgG antibodies after 2 weeks

Dengue hemorrhagic fever* *(all four of following)*
a. Clinical criteria for dengue fever, as above
b. Hemorrhagic tendency (any one of following)
   - Positive touniquet test
   - Petechiae, ecchymoses or purpura
   - Bleeding from mucosa, GIT, injection or other sites
c. Thrombocytopenia (<100,000 cells/mm^3)
d. Evidence of plasma leakage *(any one)*
   - Rise in hematocrit >20% over baseline for age/sex
   - Drop in hematocrit >20% after volume replacement
   - Signs, e.g. pleural effusion, ascites, hypoproteinemia

Dengue shock syndrome* *(both of the following)*
a. All of the above criteria for DHF *with*
b. Circulatory failure: Rapid/weak pulse, pulse pressure <20 mm Hg, hypotension, cold-clammy skin, restlessness

*As per National guidelines 2014; (DHS/DSS are not defined in Guidelines 2023).

monitoring with serial hematocrit and platelet count daily, till the patient is afebrile for 1–2 days. Cases with persistent vomiting may need parental fluids and electrolyte therapy.

Admission criteria in dengue include presence of: (a) warning signs, (b) significant bleeding, (c) persistent high fever, (d) sudden drop in body temperature, (e) rapid fall in platelet counts, (f) hypotension, and (g) organ dysfunction, e.g. renal, hepatic or CNS involvement.

Hemoconcentration due to plasma leakage from intravascular compartment is the major concern in these cases. These patients require closely monitored intravenous fluid therapy with crystalloid fluids along with supportive measures. **Fig. 10.14** presents an algorithm for fluid replacement in these cases, as per national guidelines.

Severe Dengue with Shock: These cases essentially need intensive care with close monitoring for vital signs, hematocrit and bleeding. Fluid therapy may be supplemented by colloids and if necessary, whole blood transfusions in selected cases. **Fig. 10.15** presents an algorithm for fluid replacement in these cases, as per national guidelines.

Fluid replacement therapy: Some general principles of fluid replacement therapy as follows:

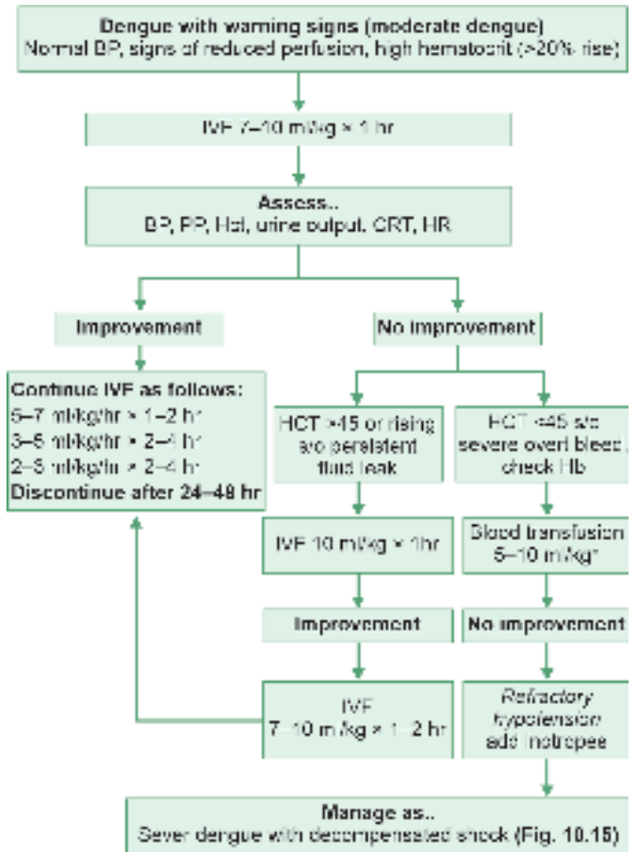

Fig. 10.14: Fluid management in moderate Dengue with warning signs.
Improvement: Hct falls, HR and BP stable, urine output rises.
No Improvement: Hct and HR rises, pulse pressure fall < 20 mm Hg, urine output falls
*Whole blood 10 ml/kg or packed cells 5 ml/kg.
IVF: IV fluids; **Hct:** Hematocrit

- Volume of fluid therapy should be calculated on the basis of body weight with 5% deficit, revised every 1–3 hours.
- First-hour fluid therapy should begin with 6 ml/kg in moderate dengue without shock and 10–20 ml/kg in severe cases with compensated shock, while those with decompensated shock must be infused 10–20 ml/kg over 15–30 minutes.
- Ringer lactate, normal saline or DNS 5% are preferred fluids for this purpose.
- Hematocrit, vital signs, e.g. heart rate and blood pressure, and urine output must be monitored along with indicators of fluid overload, e.g. hepatomegaly or breathlessness due to pulmonary edema. Central venous pressure (CVP) monitoring is advised in unstable cases, if possible.
- In cases showing improvement with falling hematocrit and stable vitals, infusion rate must be reduced gradually after every 2–4 hours. IV fluid may be discontinued after 24–48 hours.
- In cases with no improvement or deterioration, further treatment must be decided on the basis of hematocrit:
  - *In cases with rising hematocrit* suggestive of continuous plasma leak, infusion rate must be increased or maintained at 10–20 ml/kg/hr. Colloids, e.g. dextran-40, may be used in these cases.
  - *In cases with falling hematocrit*, suggestive of bleeding, blood transfusion with whole blood (10 ml/kg) or preferably packed cells (5 ml/kg) is indicated.
- Further management of non-improving cases also includes IV inotropes and cardio-respiratory support, as required.

Management of bleeding: Cases with severe bleeding are best managed with whole blood transfusion, till the specific cause is identifiable, e.g. severe thrombocytopenia or coagulopathy due to hepatic dysfunction. Platelet transfusions are recommended only in cases with: *(a) platelet count <10,000/mm^3 and/or (b) severe clinical bleeding.* Packed cell transfusions or fresh frozen plasma may be needed in some cases.

Management of organ dysfunction: Hepatitis, myocarditis and acute kidney injury is common in dengue and need to be managed intensively. Fluid therapy must be closely monitored in cases with renal dysfunction due to potential risk of pulmonary edema. Comorbidities, e.g. malaria, tuberculosis may sometimes complicate these cases and must be considered in non-responding cases.

Antiviral agents, steroids and immunoglobulins have no role in management of dengue.

Criteria for discharge in a dengue case include: (a) absence of fever >24 hours without antipyretics, (b) Stable vital signs for >2–3 days, (c) platelet count > 50,000 cells/mm^3, and (d) visible clinical improvement with no respiratory distress and good urine output.

Prevention and control of outbreaks depends on:

- *Vector-control measures*, e.g. avoidance of breeding sites, e.g. prolonged indoor water-storage and use of larvicides, insecticides.
- *Personal protection* measures, e.g. repellents, nets and avoidance of travel to outbreak area.

Currently no dengue vaccine is available in India. CYD-TDV (Dengvaxia®) is the first and only licensed vaccine against dengue, being used in some endemic countries of Asia and Latin America, though several other candidates (including one indigenous vaccine by Serum Institute of India, Pune) are under development. (Ch 9.2.4).

Other important arboviral illnesses are as follows:

Chikungunya is a benign, dengue-like syndrome, characterized by sudden onset of fever, arthralgia, maculopapular rash and leukopenia. Recent years have witnessed intermittent outbreak of this disease in many parts of India.

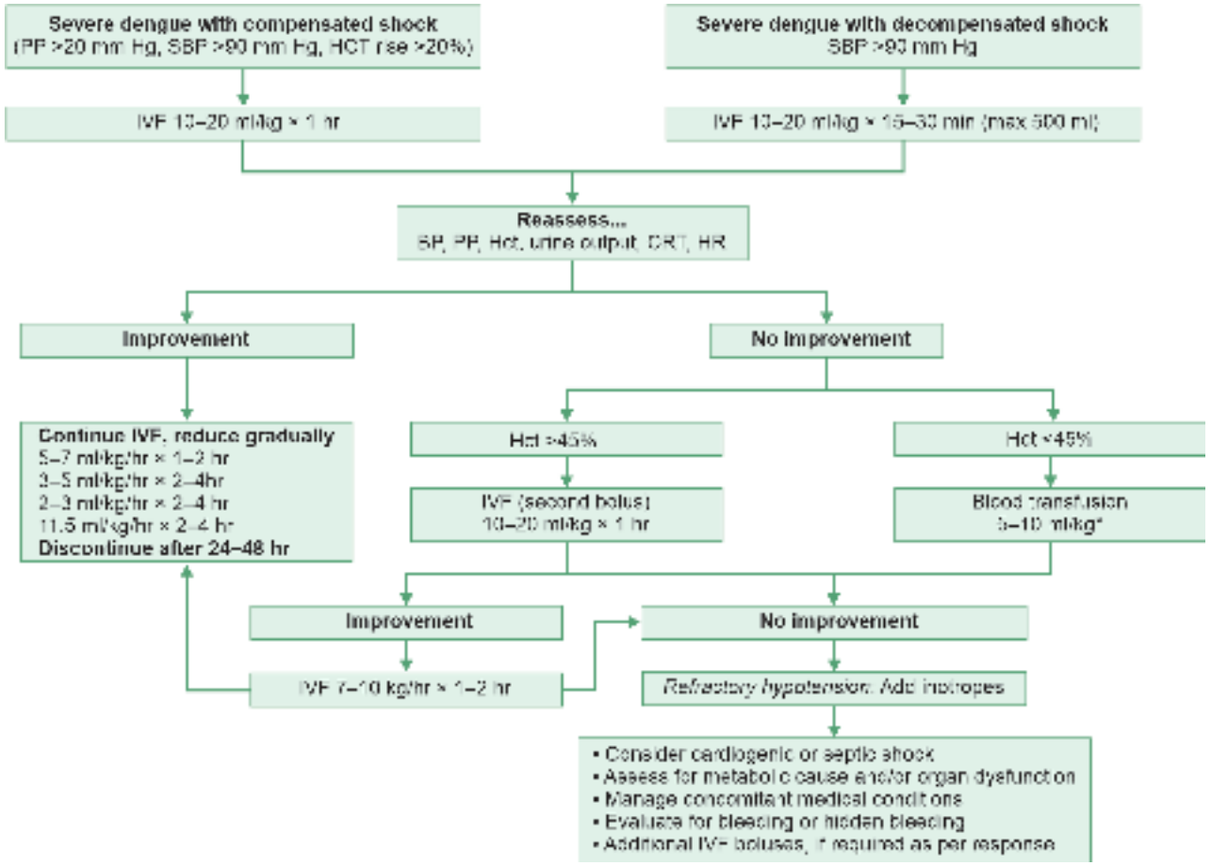

Fig. 10.15: Fluid management in severe Dengue with compensated or decompensated shock.

Improvement: Hct falls, HR and BP stable, urine output rises

No Improvement: Hct and HR rises, pulse pressure fall < 20 mm Hg, urine output falls

*Whole blood 10 ml/kg or packed cells 5 ml/kg.

IVF: IV Fluids; **Hct:** Hematocrit

Epidemiology: Chikungunya is a *zoonotic RNA virus*, widely distributed in many vertebrate species with asymptomatic or symptomatic infections. Humans are infected via mosquito bite, with *Aedes aegypti* being the commonest vector in India. Though subclinical infections are common, chikungunya outbreaks generally indicate substantial rise in susceptible human and *A. aegypti* population above a threshold level.

Clinical presentation: After an *incubation period* of 2–4 days, the infection generally follows a different course in different age-groups:

- *In infants*, clinical illness begins with sudden onset of high fever, flushed skin, conjunctival congestion and pharyngitis, followed by a generalized maculopapular rash and lymphadenopathy after 3–5 days. However, *arthralgia*-the hallmark of disease in older population, is rare in this age group. Unlike other viral infections, Enanthems are absent.
- *In older children*, acute onset fever is typically associated with severe headache, arthralgia and myalgia; followed by maculopapular rash and lymphadenopathy after 3–5 days, just before the defervescence. Febrile convulsions are common. Rash, arthralgia and lymphadenopathy disappears in next 2–3 days. Residual arthralgia beyond first week is uncommon in children.
- *In adolescents/adults*, severe *fleeting polyarthritis/* arthralgia, is the hallmark of disease. Typically, the pain shifts from joints to joints, more prominent in morning and worsens with movements. Swellings of ankle, wrist and fingers is common. Arthralgia may persist for many weeks, often confused with rheumatoid arthritis.

Diagnosis depends on: (a) history of on-going outbreak, (b) clinical suspicion, and (c) serological studies with IgM ELISA after at least a week of complaints. Viral isolation is possible though rarely feasible.

D/D includes other causes of dengue-like illnesses. Important differences with dengue include: (a) shorter duration of fever, generally <72 hours, (b) more pronounced arthralgia, terminal rash and conjunctival congestion, and (c) rarity of shock and hemorrhagic manifestations.

Treatment is largely supportive, including bed rest, NSAIDs to control pain and inflammation in cases with arthralgia, nutritional support and correction of fluid and electrolyte balance, if necessary.

Despite acute explosive onset with dengue-like illness, complications, e.g. shock and bleeding are extremely rare and mortality is almost unknown. Though older children/adolescents may continue to experience intermittent arthralgia for many months, complete recovery is the rule except a few reports of destructive arthropathy.

Prevention mainly includes mosquito control and bite prevention strategies. No vaccine is available, though a formalin inactivated and a live attenuated vaccine is in experimental stage.

Kyasanur forest disease is currently prevalent in Mysore region (Karnataka), transmitted by ticks. Monkeys or forest-rodents act as amplifying reservoirs of infection apart from human host. It mainly occurs in adults, exposed during forest-visits and presents with high fever, severe myalgia, prostration, pneumonia and bleeding. Renal/hepatic failure and meningoencephalitis may develop after a latent phase in some cases (biphasic illness). Diagnosis rests on serology and treatment is supportive.

10.24 HERPETIC VIRAL INFECTIONS

Important viral infections of genus *herpes* include: (a) herpes simplex, (b) infectious mononucleosis, (c) cytomegalovirus disease, (d) varicella-zoster or chickenpox, and (e) Roseola infantum due to HHV 6/7 infections. A relatively new herpes virus, i.e. HHV 8, identified in 1994, has been implicated in etiology of: (a) Kaposi sarcoma in AIDS, (b) multiple myeloma in elderly, and (c) other malignancies, e.g. lymphoma in immunodeficient host.

A distinguishing features of all herpetic infections is the life-long persistence of virus after primary infection (*latent phase)* with intermittent *reactivation* or viral shedding.

10.24.1 HERPES SIMPLEX

Herpes simplex (HSV) infections are caused by two strains—HSV_1, which commonly infects skin and mucus membranes; and HSV_2 that mainly infects genital tract.

Epidemiology: HSV_1 is transmitted by close human contact, while HSV_2 is transmitted by direct sexual or genital-hand-genital contact. Newborns are usually infected during their passage through infected birth canal (*perinatal* infection), rather than transplacentally.

HSV_1 infections are common in early childhood in overcrowded living conditions, while HSV_2 usually infects in adolescence. A breech in skin/mucosal continuity facilitates HSV entry.

Pathogenesis of HSV infections may be divided into 3 stages—(a) primary infection, (b) latent infection, and (c) reactivation of latent infection *or* secondary infection with other serotype (HSV_1 > HSV_2 or vice versa).

- *Primary HSV infection* is usually asymptomatic or limited to localized skin/mucosal lesions. Sporadic encephalitis is perhaps the only systemic manifestation of primary HSV infection.
- *Latent phase:* After primary infection, inactive HSV always persists life-long in ganglions as latent infection, with intermittent clinical reactivation or virus shedding.
- *Re-activation* is usually precipitated by *external stimuli*, e.g. cold or ultraviolet rays exposure or *internal stimuli*, e.g. fever, emotional stress and menstruation.
- *Secondary infection* is usually asymptomatic except the risk of perinatal transmission. All infections, whether primary, reactivation or secondary, in an immunocompromised host, i.e. newborn, malnutrition, malignancies and AIDS, may produce severe invasive disease.

Clinical manifestations: *Grouped vesicular lesions* are hallmark of primary as well as reactivated HSV disease, presenting as follows:

- *Skin lesions* (HSV_1) are characterized by grouped thin-wall vesicles with erythematous base, which rupture, scab and heal within 7–10 days without scarring. Eruptions may be preceded by local pruritus or neuralgic pain and more common at the site of trauma/irritation, e.g. contact dermatitis. Herpetic whitlow involving fingers is commonly seen in thumb-sucking children.
  - *Mucosal lesions* (HSV_1) manifest as—(i) *herpetic gingivostomatitis*, i.e. acute onset of painful oral ulcers with drooling and high fever, lasting for 7–14 days, (ii) *herpes labialis*, i.e. perioral grouped vesicles on or near lips, or (c) *ocular lesions*, e.g. keratoconjunctivitis.
  - *Genital lesions* (HSV^2) are mostly seen in adolescents as vesicles/ulcers over vulvovaginal region or penis.
  - *CNS infection*, e.g. encephalitis or aseptic meningitis with/without mucocutaneous lesions are common even in immunocompetent children. HSV_1 is a leading cause of sporadic encephalitis in India with acute necrotizing infection of frontotemporal cortex and limbic system.

HSV in immunocompromised children may present with chronic/recurrent orogenital lesions *or* invasive disease, e.g. sepsis, hepatitis, DIC, pneumonitis or esophagitis.

Perinatal HSV infection is acquired *in utero* (<5%), during vaginal passage (~ 80%) or as postnatal nosocomial infection, discussed in Ch 12.15.4.

Diagnosis depends on: (a) characteristic grouped vesicular lesions, (b) virus detection by PCR or tissue

culture, (c) serology, or (d) typical histology, i.e. multinucleated giant cells and intranuclear inclusion bodies on *Tzanck* staining of vesicle scrapping, CSF or tissue biopsy.

Treatment: IV Acyclovir therapy is the mainstay of treatment in HSV infections, either orally (60 mg/kg/day q6hr for 7 days, maximum 200 mg/dose) for localized skin/mucosal lesions or intravenously (30 mg/kg/day q8hr slowly for 21 days) for encephalitis or invasive disease, apart from supportive care. Long-acting valacyclovir (500 mg BD) or famciclovir (125 mg BD) for 3–5 days may be used in adolescents with genital lesions. Half of these doses may be used for reactivation lesions (for 5 days) or prophylaxis for recurrent lesions in immunocompromised host.

10.24.2 INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis is a clinical illness characterized by acute fever, sore throat and generalized lymphadenopathy, along with presence of atypical lymphocytes in blood. Over 90% cases are caused by *Epstein-Barr virus* (EBV). Remaining may be due to other *viruses*, e.g. CMV, adenovirus, rubella, HIV, etc. or *parasites*, e.g. toxoplasma.

Epidemiology: EBV is intermittently excreted in oropharyngeal secretions of the infected person (reservoir) and transmitted by close contact, e.g. kissing. Primary infection is common in children <3 years and usually remains dormant except intermittent viral shedding throughout life. Clinical disease denotes either primary infection or reactivation of latent infection.

On entry, EBV replicates in oral epithelial cells and salivary glands, followed by viremia with disseminated infection of B-lymphocytes and lymphoreticular system. Characteristic *atypical lymphocytes* in these cases are actually CD_8 lymphocytes, formed to prevent the spread of infected B-cells. Infection persists life-long in oropharyngeal cells and B-cells, to re-activate any time, specially in immunocompromised states.

Clinically EBV infection is mostly asymptomatic, though symptomatic disease, i.e. *infectious mononucleosis* presents after an incubation period of 4–6 weeks, with:

- *Prodromal phase* with mild fever, malaise, headache, myalgia, sore throat and abdominal pain for 1–2 weeks.
- *Characteristic phase* with—(i) progressively rising fever, (ii) sore throat, (iii) generalized lymphadenopathy (90%), (iv) splenohepatomegaly, and (v) maculopapular rash (5–15%). Epitrochlear lymphadenopathy and development of rash on ampicillin therapy are useful indicators of infectious mononucleosis.
- *Convalescence* in 6–8 weeks with spontaneous recovery except in immunodeficient cases.

Complications are uncommon, usually seen during 2nd–3rd weeks of illness **(Table 10.41)**. Splenic rupture is the most dreaded complication in these cases.

TABLE 10.41: Complications of infectious mononucleosis

- Splenic rupture
- *Respiratory:* Pneumonia, obstruction (? adenoids)
- *Neurological:*
  - Aseptic meningitis,
  - Acute cerebellar ataxia
  - Guillain-Barré syndrome
  - Alice in wonderland syndrome**
- *Hematological**: Anemia, thrombocytopenia

*autoimmune or due to bone marrow depression
**loss of perceptual capabilities

Diagnosis must be suspected in a clinical triad of *prolonged fever, pharyngitis and generalized lymphadenopathy,* supported by:

- *Lymphocytosis with atypical lymphocytes* (larger lymphocytes with eccentric, large, indented nucleus and lower nuclear-cytoplasm ratio). Other causes of atypical lymphocytosis include: CMV, toxoplasmosis, rubella, roseola, mumps, viral hepatitis, mycoplasma, and drugs.
- *Paul-Bunnell-Davidsohn test,* for presence of *nonspecific* heterophile IgM antibodies with titers <1:28 taken as positive. A rapid qualitative slide test (*mono-spot*) based on similar principles is available to detect EBV infection in >50–90% cases.
- *Specific EBV antibodies* tests, anti-VCA (viral capsid antigen) or anti-EA (early antigen) antibodies detect early infection, while anti-EB nuclear antigen antibodies are positive in convalescent phase or due to previous infection.
- *Viral culture* from oropharynx is positive for ~ 1 year after primary infection or during intermittent shedding.

Treatment is non-specific, including *supportive measures* like bed rest, antipyretics and avoidance of splenic trauma.

Steroids (PO prednisolone 1 mg/kg/d × 2 weeks) are indicated only in complicated cases with – (i) severe airway obstruction, (ii) symptomatic thrombocytopenia, (iii) autoimmune hemolytic anemia, and (iv) aseptic meningitis.

High doses of acyclovir with/without steroids reduce viral shedding but do not affect the severity or course.

Prognosis is excellent with complete recovery in 4–8 weeks in absence of acute complications and recurrence in unknown. Rare case may develop chronic active EBV infection with progressive immunodeficiency and often succumb to opportunistic infections, hemophagocytosis, multiorgan failure, or EBV-positive lymphomas. Stem cell transplantation is the only option in cases of chronic active EBV infection with complications.

Prevention involves avoidance of contact with an infected case and no vaccine is available at present. Contact sports should be avoided to prevent splenic rupture.

Note: EBV was the first virus found to be associated with malignancies and has been implicated in:

- *Benign lymphoproliferative illnesses, e.g. hemo-phagocytic syndrome, oral hairy leukoplakia and lymphocytic interstitial pneumonitis (LIP) in AIDS.*
- *Malignancies, e.g. Burkitt's lymphoma, Hodgkin disease, nasopharyngeal carcinoma, leiomyosarcoma.*

10.24.3 CYTOMEGALOVIRUS DISEASE

Cytomegalovirus (CMV) is the *largest herpes virus*, present in body fluids of an infected person, (e.g. saliva, urine, milk, stool and blood) and transmitted by close person-person contact.

While primary infection in early childhood is very common and almost always asymptomatic, it persists life-long with potential risk of reactivation. CMV infection in newborn (Ch. 12.15.4) or immunocompromised states is associated with high mortality and morbidity.

Clinical presentation of CMV infection varies with age and immune status.

- *In immunocompetent children,* CMV infection is almost always asymptomatic, rarely presenting as mild infectious mononucleosis-like illness.
- *Perinatal CMV or postnatal infection in immuno-compromised host,* may present with serious systemic illnesses, e.g. pneumonitis, hepatitis, chorioretinitis, leukopenia/thrombocytopenia, enteritis, or pro-gressive encephalitis.

Diagnosis of active infection rests on: (a) detection of virus in urine, saliva or other secretions/infected sites by PCR or DNA hybridization techniques, *or* (b) serology, i.e. elevated anti-CMV IgM titers or rising IgG titers after 4 weeks.

Treatment with IV ganciclovir (2.5 mg/kg/dose TDS for 3–6 weeks), is indicated only in infected newborns or immunocompromised host with severe disease. PO valganciclovir may be more effective and less toxic than IV ganciclovir, if available.

Prolonged prophylaxis with ganciclovir or valganci-clovir is indicated in cases of transplant recipients and AIDS with CD4 count <100 cells/mm^3.

10.25 COVID-19 INFECTION

Despite the lesser incidence and severity, SARS-CoV-2 (COVID-19) infection in children posed unique challenges during the pandemic due to large pool of asymptomatic cases to facilitate spread of infection, different modes of presentation, e.g. multi-systemic inflammatory syndrome (MIS-C) and long-term effects on their physical and mental health, education and immunization status.

Children <19 years of age contributed to ~10% of reported COVID-19 cases but with <5% of hospitalizations and <0.5% of mortality, globally as well as in India.

Epidemiology: Children usually contract infection from a household contact (75–90%), rarely from other in schools, child-care centers or health-care settings. Infected children, even if asymptomatic, have higher nasopharyngeal viral loads than adults and shed the virus for a longer period.

Pathogenesis: SARS-CoV-2 is transmitted as droplet infection or by contaminated fomites and surfaces. On entry, virus gets attached to angiotensin converting enzyme-2 (ACE_2) receptors present on the ciliated respiratory epithelium and gastrointestinal mucosa. After local replication, viremia develops followed by development of either appropriate immune response to clear the virus or dysregulated immune response with development of cytokine storm – responsible for clinical deterioration with acute respiratory distress syndrome (ARDS), multi-organ failure and sometimes, death. It is also characterized by elevation of inflammatory markers, e.g. CRP, procalcitonin, interleukin ($IL_{6/10}$) and D-dimer levels, also leading to increased thrombosis. Patients may also have abnormal coagulation parameters due to high expression of ACE_2 receptors in vascular endothelial cells.

Children usually have milder disease, due to: (a) immaturity of ACE_2 receptors, (b) relatively immature immune system, unable to mount intense inflammatory response and cytokine storm. However, children <1 year or with underlying medical conditions, e.g. obesity, immunocompromised states, chronic lung/heart disease, diabetes or other metabolic diseases are at higher risk of severe disease.

Clinically, while ~15–20% cases are asymptomatic, rest present after an incubation period of ~4–6 days with fever, upper respiratory infection, myalgia, diarrhea and vomiting as initial symptoms. Further course may be classified as follows:

- *Mild cases*, presenting as uncomplicated upper respiratory infection with fever, sore throat, rhinorrhea, cough and breathlessness, which usually recover in 1–2 weeks.
- *Moderated cases* progressing to non-severe pneumonia with tachypnea but without severe hypoxia or danger signs and SpO_2 ranging between 90–94% in room air.
- *Severe COVID* cases develop severe pneumonia with *danger signs,* e.g. inability to breastfeed or drink, grunt-ing, severe lower chest in drawings, cyanosis, lethargy, somnolence, or *organ dysfunction* with ARDS, septic shock, coma and/or seizures and MODS.

Diagnosis: RT-PCR test to detect presence of SARS-CoV-2 nucleic acid from nose and throat swab is the gold standard for diagnosis, though the sensitivity varies from 60–70%. Rapid antigen test may be used in symptomatic cases (only) with sensitivity of 40–50%, if RT-PCR is not available. HRCT of the chest is not recommended for

diagnosis in children. However, Chest X-ray is required in cases with lower respiratory symptoms to exclude other cases.

Moderate to severe cases with COVID-19 need monitoring for inflammatory markers, e.g. CRP, procalcitonin, interleukin (IL_6), TNF-α, D-dimer assay, etc.

Management: Immediate swab collection (preferably nasal) is recommended in all suspected cases for diagnosis with RT-PCR or RAT (if symptomatic), along with initiation of infection prevention control measures, e.g. isolation, hand hygiene, use of personal protective equipment (PPE), safe waste management and disinfection of equipment as per guidelines. Further management depends on the severity of disease as follows:

Mild cases can be managed at home with symptomatic treatment with paracetamol and adequate feeds/fluids, without antibiotics or antiviral drugs. Parents should be counseled about COVID-appropriate behavior, watch for danger signs and report in cases of worsening.

Moderate cases with non-severe pneumonia must be hospitalized with:

- Oxygen therapy with nasal cannula (<4 L/min) or face mask (<6 L/min) to maintain SpO_2 as 94–98%.
- Supportive therapy to ensure adequate nutrition as well as fluid and electrolyte balance.
- Antibiotics, *only* if there is a strong suspicion of bacterial infection
- Steroids, *only* if rapid deterioration and >5 days have passed since onset of disease.
- *Monitoring* for deterioration of clinical status (respiratory distress, hypotension) and SpO_2,
- Communication with parents to alleviating anxiety and ensure COVID-appropriate behavior.

Severe cases with severe pneumonia and *danger signs* or *organ dysfunction* must be transferred to intensive care unit for continuous monitoring and managed with:

- Oxygen therapy with targeted saturation of 94–98%, using high-flow nasal cannula or HFNC (2 L/kg/min) or non-rebreathing mask or NRBM (10–15 L/min) to provide ~100% FiO_2.
- Ventilatory support using low tidal volume (4–8 ml/kg) with optimum positive end-expiratory pressure (PEEP) to keep P plateau <28 cm H_2O and driving pressure <15 cm H_2O. Use of cuffed endotracheal (ET) tube, in-line suction with minimal disconnection of ventilator circuits and early-proning should be considered in children with severe ARDS.
- Supportive therapy to ensure adequate nutrition as well as fluid and electrolyte balance. Children with shock must be managed with isotonic crystalloid boluses, inotropes and hydrocortisone (IV 2–4 mg/kg/24 hours) for catecholamine-resistant cases, if they are not on steroids. Fluid restriction may be needed in cases with ARDS/MODS.
- Empiric antibiotics, as per the hospital policy after collection of blood cultures.
- Steroids if >5 days have lapsed since the onset of symptoms with a increasing oxygen demand on HFNC, NRBM, non-invasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation with Dexamethasone 0.15 mg/kg (maximum 6 mg) or Methylprednisolone 0.75 mg/kg OD (maximum 30 mg) for 5–7 days.
- Antivirals, e.g. R*emdesivir*: are not recommend in children but may be considered in hospitalized cases with emergent/increasing need for supplemental oxygen and: (a) age 16 years, (b) age 12 years with presence of the high-risk factors for severe disease, and, (c) age < 12 years in consultation with pediatric infectious disease specialist. A 3–5 day course of remdesivir (IV 5 mg/kg, to maximum 200 mg over 30–120 min followed by 2.5 mg/kg to maximum 100 mg daily single dose for 3–5 days) early in the disease has shown up to 87% reduction in deaths. There is no role for remdesivir beyond 10 days of infection, and can cause hepatic derangement.
- *Prophylactic anticoagulation* is not routinely recommended except in hospitalized children with: (a) strong personal/family history of venous thromboembolism, (b) indwelling central venous line with additional risk factors, (c) D-dimer >5 times of upper limit, and (d) children already on anticoagulation therapy. Low molecular weight heparin may be used as SC 0.5 mg/kg twice daily till discharge, provided there is no renal dysfunction cases with confirmed thrombosis need therapeutic anticoagulants, i.e. low molecular weight heparin as SC 1 mg/kg twice daily for ~12 weeks.
- Transfusions is indicated in children with < 7 g/dl with stable oxygenation and hemodynamics or <10 g/dl for those with refractory hypoxemia or shock.
- Intensive monitoring is needed in all cases for vital signs, inflammatory markers, blood gases and coagulation profile.

Management of the Newborn of COVID-19 Infected Mothers

All COVID positive deliveries should be conducted preferably in dedicated centers with standard infection containment protocols. IAP recommends that:

- Neonatal resuscitation should follow standard guidelines, using appropriate COVID-protective measures. Risk of postnatal infection in the baby may be reduced if mothers wear a triple-layer mask and adheres to respiratory etiquettes.
- Mother-infant dyads should be roomed-in and exclusive breastfeeding should be encouraged, regardless of maternal COVID-19 status.
- Kangaroo care is recommended for low birth weight neonates, regardless of the COVID-19 status of the mother or neonate.

- Symptomatic/neonates should be isolated with mother in a designated area, segregating suspect and confirmed cases.
- All forms of respiratory support are at risk of generating aerosols and HCWs must wear appropriate PPE, preferably in a negative air pressure area.
- Baby should be tested as follows:
  - *Within 24–48 hours*, if mother tested positive within 14 days before or 2 days after delivery. However rooming-in should not be delayed. Repeat testing is advised in asymptomatic newborns before discharge to prevent further transmission.
  - *Within 5th-7th day*, if mother or a family member/HCW dealing with baby is exposed to a COVID positive case,
  - *Immediately* in all symptomatic neonates, which may be repeated after 24–48 hours, if first report is negative despite strong suspicion.
- Neonates with asymptomatic or mild disease require no additional laboratory tests and stable mother/baby dyad may be discharged after 24–48 hours but must be followed-up for 14–28 days.
- All moderate to severe cases must be investigated and managed as per regular protocols with full infection control measures.

Multisystem Inflammatory Syndrome in Children (MIS-C)

MIS-C, also termed as pediatric inflammatory multisystem syndrome (PIMS), is a rare but life-threatening complication of COVID-19 infection in children, characterized by hyperinflammatory syndrome with involvement of multiple organs, usually seen after 2–6 weeks of acute infection.

Diagnosis of MIS-C depends on fulfillment of all six parameters included in WHO diagnostic criteria 2020 **(Table 10.42)**.

Investigation depends upon severity of disease and include:

- ***Tier-1 screening*** in all cases on admission including – CBC, CRP, ESR, liver and renal function tests, blood sugar, blood gas analysis, and SARS-CoV-2 serology/RT-PCR. Tier-one screen is considered as positive if both of these criteria are fulfilled:
  - CRP > 5 mg/dl and/or ESR > 40 mm/hour
  - *At least one of these*: Absolute lymphocyte count (ALC) < 1,000/µl, platelet count < 150,000/µl, Na < 135 mEq/L, neutrophilia, and hypoalbuminemia
- ***Tier-2 tests*** are required in cases positive on tier-one screening and include: ECG, echocardiogram, B-type natriuretic peptide (BNP), troponin-T, ferritin, lactate dehydrogenase, procalcitonin, interleukin 6 (IL-6), prothrombin time, activated partial thromboplastin time, D-dimer, and fibrinogen.

TABLE 10.42: WHO criteria for MIS-C (All Six)

- Age 0–19 years
- Fever > 3 days
- Clinical signs (any two)
  - Rash, bilateral non-purulent conjunctivitis, or mucocutaneous inflammation signs (mouth, hands or feet)
  - Hypotension or shock, cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP)
  - Evidence of coagulopathy (prolonged PT/PTT, elevated D-dimer)
  - Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
- Elevated markers of inflammation e.g. ESR, CRP or procalcitonin
- No other obvious microbial cause of inflammation, including bacterial sepsis, toxic shock syndromes or tropical infectious diseases, i.e., malaria, dengue etc.
- Evidence of COVID-19 infection: positive RT-PCR/RAT or Serology or contact with an individual with COVID-19

(**BNP:** B-type natriuretic peptide; **CRP:** C-reactive protein; **ESR:** Erythrocyte sedimentation rate; **PT:** Prothrombin time; **PTT:** Partial thromboplastin time; **RAT:** Rapid antigen test)

A child is considered to have MIS-C only if: (a) both, Tier 1 and 2 tests are positive, and (b) other causes or tropical infections have been excluded. Isolated elevated COVID-19 antibodies are *not synonymous* with MIS-C.

Management: For management, MIS-C may be classified into four categories:

1. *MIS-C without shock;*
2. *MIS-C with shock* (tachycardia, hypotension, requiring fluid bolus 30 ml/kg, or inotropic support) or MODS with two or more organ involvement;
3. *MIS-C with Kawasaki phenotype,* meeting complete/incomplete Kawasaki disease criteria **(Table 24.11)**;
4. *MIS-C with refractory disease,* not responded to first-tier therapy with IVIG and low-dose steroids within 48 hours.

Important components of management include: (a) stabilization in terms of ventilation and perfusion, (b) treatment of organ dysfunction, (c) anti-inflammatory therapy, (d) monitoring for disease progression, and (e) long-term follow-up for complications.

- ***Anti-inflammatory therapy*** to reduce tissue inflammation or prevent progression of myocardial dysfunction usually includes: IVIG (2 gm/kg maximum 100 gm) infusion over 8–12 hours along with low-dose IV Methylprednisolone (2 mg/kg/day), slowly switching to PO prednisolone and tapered over 2–3 weeks. While only Methylprednisolone (without IVIG) is enough in cases without shock, oral low-dose Aspirin (PO 3–55 mg/kg/day) must be added in those with Kawasaki phenotype.

In children with refractory MIS-C despite above treatment, IV/SC Anakinra (>4 mg/kg/day) can be

used after expert consultation. *Infliximab/tocilizumab* are not recommended in children.

- ***Anticoagulation:*** MIS-C with documented thrombosis, ejection fraction < 35%, coronary artery Z score ≥ 10 or giant aneurysm with diameter > 8 mm need anticoagulation with low molecular weight heparin SC 1 mg/kg/dose (0.75 mg/kg/dose in <2 months) for 2 weeks after discharge. Low-dose aspirin (PO 3–5 mg/kg/day; max 80 mg/day) should be used if platelets >80,000/µl and continued till normal coronary arteries are confirmed at 4 weeks after diagnosis.

Outcome: Mortality rate is 1–2%, higher in cases with delayed diagnosis/treatment. Late complications include coronary artery aneurysm (25%), cardiac dysfunction, renal involvement and systemic thrombosis.

10.26 INFLUENZA

Influenza is a highly contagious viral illness of respiratory tract with seasonal outbreaks (seasonal influenza) and intermittent pandemics (pandemic influenza). *Seasonal influenza* is common in winter season and outbreaks tend to subside after 4–6 weeks with low morbidity and mortality.

Pandemic influenza refers to particularly contagious strains of virus that spread rapidly to create a worldwide pandemic. Latest global pandemic by novel influenza strain (H1N1) was originated in USA and initially affected pigs (Swine flu). India was affected soon after in 2009, though it has gradually weakened now with development of herd immunity.

Etiology: Influenza is a large RNA virus of family Orthomyxoviridae, with three major serotypes affecting humans—A, B, and C. While all pandemics have been caused only by serotype A, seasonal outbreaks are usually due to A and B serotypes. Type C virus is responsible for sporadic and mild upper respiratory tract infections.

Serotype A is further classified on the basis of two surface proteins—hemagglutinin (HA) and neuraminidase (NA) and strains are named on the basis of the combination of HA and NA proteins, e.g. H1N1, H2N2, H3N2, etc.

On-going global pandemic has been caused by H1N1 infection, though seasonal outbreaks due to H3N2 serotype B infections are common.

Epidemiology of influenzae virus is interesting, as prevalent serotypes during outbreaks are known to change every year, due to minor antigenic changes following point mutations, termed *antigenic drift,* seen in both A and B serotypes. Infrequently, subtypes changes dramatically due to reassortment of viral gene segments, resulting in emergence of novel subtypes by the process termed *antigenic shift,* seen only in serotype A.

Pathogenesis: Human influenza virus is usually transmitted as a droplet infection from the infected host and enters the host cells through specific cell-surface virus receptors, mostly located in upper respiratory tract. In usual cases of seasonal influenza, viral replication remains limited to upper respiratory tract, while extension to lower airways and lung parenchyma contributes to more serious illness with pneumonia and ARDS. Each infection leaves behind the strain-specific immunity, but re-infections due to similar strains are common due to antigenic drifts.

Pathology involves direct tissue damage as well as immune-mediated inflammatory damage, due to release of pro-inflammatory cytokines, e.g. IL-6 and interferon. While direct viral damage is essentially confined to upper respiratory tract or airways, pneumonia, ARDS and systemic damage is usually caused the *cytokine storm*. Secondary bacterial pneumonia is common.

Clinical spectrum: *Season influenza* is more common in younger population, usually presenting as *influenza like illness* (ILI). Severe disease or mortality is rare except at extremes of age.

Influenza-like illness (ILI) usually begins as a non-specific respiratory viral illness after an incubation period of 1–3 days (maximum 7 days), with fever, sore throat, cough, nasal congestion, malaise headache, myalgia and loss of appetite. Nausea, vomiting and diarrhea may also develop. Most cases recover spontaneously within a week. Over 1/3rd of infections are asymptomatic.

Complications are rare except in high-risk cases, e.g. young infants or those with cardio-respiratory disease, hemoglobinopathies and immunocompromised states; and include acute hemorrhagic pneumonia, myocarditis, myositis, toxic-shock syndrome and rarely, neurological complications including Guillain-Barré syndrome.

Diagnosis must be suspected on epidemiological and clinical considerations. Confirmation usually depends on RTPCR, though rapid diagnostic tests are available with poor sensitivity (10–80%) but higher specificity (95–100%). Specimen for laboratory diagnosis must be obtained by multiple swabs from nasopharynx, throat or trachea and must be transported in specific liquid media with reverse cold-chain.

Viral cultures are possible and serodiagnosis with fourfold rise in specific neutralizing antibodies may be used for epidemiological studies.

Management depends on categorization of cases according to the severity of illness and a risk-based approach for home isolation, testing, treatment and hospitalization has been recommended by Government of India 2015, updated 2022 **(Table 10.43)**, some important steps in the management include:

a. Category A cases must be managed at home with isolation measures and supportive therapy including bed rest, adequate hydration and antipyretics, e.g.

TABLE 10.43: Categorization, diagnosis and management of seasonal influenza (Governement of India Guidelines 2015)

	Category			
	A	***B1***	***B2***	***C***
Symptoms	Mild fever *and* cough/sore throat *with/without* bodyache, headache, diarrhea, vomiting	***Category A with*** High fever + severe sore throat	***Category A with*** High-risk group, e.g. • Children with risk factors* • Pregnancy • Age >65 years	***Category A or B with*** Breathlessness, chest pain drowsiness, hypotension, hemoptysis, cyanosis ***Red-flag signs (children):*** Somnolence, poor feeding, seizures, breathlessness worsening of underlying condition
Diagnostic testing	No	No	No	Yes
Management	Home isolation No Oseltamivir	Home isolation Oseltamivir		Hospitalization Oseltamivir

***Risk factors:** Underlying lung disease, heart disease, liver disease, kidney disease, blood disease, neurological disorders, cancer, diabetes, HIV/AIDS, long-term steroid therapy

paracetamol. Aspirin should be avoided due to potential risk of Reye syndrome. All home managed cases should be reviewed after 24–48 hours for any change in the severity. Antibiotics may be used, if required as per community-acquired pneumonia guidelines.

b. ***Category B cases*** can also be managed at home, like category A, but with antiviral therapy without viral testing, discussed below.

c. ***Category C cases*** should be hospitalized and managed in isolation with infection control measures, along with fluid and electrolyte therapy, parenteral nutrition, oxygen/ventilatory support, cardiovascular support and antibiotics for secondary infection.

Antiviral therapy with *PO Oseltamivir* for 5 days is indicated only in category B and C disease and should be started preferably with 48 hours of the onset of symptoms, as follows:

- *Infancy age-wise:* <3 months: (12 mg BD), 3–5 months: (20 mg BD); 6–11 months (25 mg BD)
- *Post-infancy weight-wise:* <15 kg (30 mg BD), 15–23 kg (45 mg BD), 24–40 kg (60 mg BD) and >40 kg (75 mg BD).

Alternative therapy with other neuraminidase inhibitors, e.g. zanamivir and peramivir, is not approved in children <5 years.

Prevention involves general measures to prevent spread of airborne infections and vaccination of high-risk cases. *Chemoprophylaxis* or presumptive treatment with Oseltamivir, in close household contacts has been used but generally not recommended in children.

IAP recommends influenza vaccine to all children from 6 months to 5 years of age and to high-risk children beyond this age including those with – chronic cardiac, pulmonary (excluding asthma), hematologic, renal (including nephrotic syndrome) and liver disease and diabetes mellitus, and immunodeficiency states. Currently available influenza vaccines are inactivated trivalent or Quadrivalent vaccines containing WHO recommended strains. All of them include H1N1 strain **(Fig. 9.2.2)**. Two doses of vaccines are recommended in the first year (after 6 months of age), followed by single dose annually before the onset of season.

Some other influenza-like illnesses (ILI) are as follows:

Rhinovirus infections: Although no age is immune, these infections are more common in young children and during winter or late summer season.

Clinical spectrum: Apart from *common cold*, the commonest manifestation (Ch 16.5.1), rhinoviral infections are associated with—(a) pneumonia in very young children, (b) acute asthmatic exacerbations in schoolchildren, and (c) chronic bronchitis in adults.

Treatment is symptomatic. Antiviral drugs do not seem to affect the course or severity of disease.

Parainfluenza viruses have four serotypes, of which seasonal outbreaks in summer/rainy season are usually due to type 1 and 2, while type 3 is endemic.

Clinical spectrum: Fever is typically *uncommon* in parainfluenza infections, which may present with: (a) acute laryngotracheobronchitis or croup (commonest cause), (b) acute bronchiolitis or bronchitis, and (c) persistent pneumonia in an immunocompromised host.

Treatment is symptomatic and specific antiviral therapy with *Ribavarin* is indicated only in immunocompromised children.

Adenovirus infections, usually due to three serotypes (1, 2, 5), are more prevalent in spring and winter season and many states have witnessed outbreaks of respiratory

TABLE 10.44: Clinical spectrum of adenoviral infections

• *URTI*	:	Pharyngitis, pharyngoconjunctival fever
• *LRTI*	:	Pertusis-like syndrome, pneumonia*
• *Eye*	:	Epidemic keratoconjunctivitis, follicular conj.
• *Cardiac*	:	Myocarditis, cardiomyopathy
• *GIT*	:	Acute diarrhoea, intussception
• *Hepatic*	:	Reye's-like syndrome, hepatitis*
• *Renal*	:	Hemorrhagic cystitis, interstitial nephritis*
• *CNS*	:	Chronic meningoencephalitis*

*in immunocompromised host only.

adenoviral infections in 2022–23, often indistinguishable from influenza or COVID-19 infections.

Clinical spectrum of these infections is very wide **(Table 10.44)**, the commonest being acute upper respiratory or conjunctival infections. Adenoviruses are most common cause of follicular conjunctivitis and epidemic keratoconjunctivitis.

Pharyngoconjunctival fever is a distinct presentation of adenoviral 3 infection, characterized by high fever, pharyngitis, conjunctivitis and cervical lymphadenopathy, lasting for 3–5 days.

Diagnosis, apart from viral studies, is supported by characteristic histology, i.e. dense lymphocytic infiltrates, destruction of bronchiolar epithelium, focal necrosis of mucosal glands, hyaline membrane formation and nuclear inclusion bodies.

Treatment is non-specific, although Ribavarin has been used on immunocompromised cases.

Prevention: A monovalent vaccine is available for US military recruits, but not for general use.

Respiratory syncytial virus (RSV) infections are most common in infancy, during winter season or as nosocomial outbreaks.

Clinical spectrum: RSV infections are commonest cause of: (a) acute bronchiolitis, apart from causing, (b) acute laryngotracheobronchitis (croup) and rarely, (c) pneumonia in high-risk infants, e.g. those with cyanotic heart disease, bronchopulmonary dysplasia or severe immunodeficiency.

Treatment is symptomatic, though Ribavarin aerosol therapy has been used with modest effect on RSV pneumonia in high-risk cases.

Prevention: No vaccine is currently available, but passive prophylaxis with '*Palivizumab*'—a monoclonal antibody, or *RSV-enriched IVIG* is recommended in high-risk cases with chronic cardiopulmonary disease.

10.27 RABIES

Rabies is an easily preventable but essentially fatal CNS infection that continues to be a major public health problem in India, accounting for >50% of total world cases. *Union territories of Lakshadweep and Andaman/Nicobar islands are free from this disease.*

Epidemiology: Rabies, caused by a neurotropic bullet-shaped RNA virus—*Lyssavirus seortype 1*, is primarily a zoonotic disease of warm-blooded animals. Man is accidentally affected after bite or licks of rabid animals. Dog is the commonest source (99%) in India, though rare cases may involve cats and wild canines, e.g. fox and wolves. Vampire bat-related rabies, common in USA and Latin America, is not reported from India. Barring few anecdotal reports, there is no asymptomatic carrier state and infection is essentially fatal in animals.

Virus is secreted in saliva of rabid animal only from 3–6 days before the onset of symptoms and hence, human infection is unlikely if the dog survives or remains well till 10 days of biting incident. Less than 50% bites by proven rabid animals result in human rabies. Human-to-human transmission, though theoretically possible, is extremely rare.

Pathogenesis: After inoculation with contaminated saliva, virus replicates in muscles or connective tissue. Unless neutralized at this stage by natural or vaccine induced immune response, it eventually and irreversibly gets attached to the peripheral nerves and development of disease becomes inevitable. Virus spreads centripetally within neuronal sheaths to CNS, mainly involving brainstem, basal ganglia, thalamus and hippocampus, but *sparing* cerebral cortex (no loss of consciousness).

Neuronal destruction at brain-stem level, including inhibitory neurons to nucleus ambiguous that controls inspiration, is responsible for classical presentation of hydrophobia and inspiratory muscle spasms. Following CNS infection, virus also descends centrifugally along the nerves to distal muscles, skin and saliva.

Clinical manifestations: Incubation period is extremely variable, ranging from 4 days to 7 years (usual: 20–60 days), being *shorter* in children, facial bites and after severe mauling. Clinical progression is also variable, but may be divided into:

- ***Prodromal phase*** (2–10 days), with—(i) pain, pruritus or paresthesias at wound site, (ii) mental changes, e.g. apprehension, anxiety or agitation and (iii) non-specific symptoms, e.g. mild fever, headache, vomiting, etc.
- ***Acute neurological phase*** (2–21 days) is of furious (80%) or paralytic (20%) variety, characterized by:
  - *Pathognomonic hydrophobia or aerophobia*, i.e. reflex spasms of pharyngeal and neck muscles, during swallowing, wind-movement, etc.
  - *Intermittent bizarre hyperactivity* or combative activity in furious variety, with intervening lucid periods and typical apprehensive appearance.
  - *Ascending asymmetrical flaccid paralysis*, in paralytic variety.
- ***Terminal phase***, characterized by increasing frequency of unprovoked spasms, opisthotonus, labored

breathing, hypoxic coma and ultimately, cardiorespiratory arrest. Death is inevitable, though a few unconfirmed survivors have been reported among those who were vaccinated *before* the exposure.

Diagnosis is mainly clinical, based on history of dog bite and typical presentation. Antemortem laboratory diagnosis, though rarely needed, is possible by:

- Antigen detection using fluorescent antibodies (immunofluorescence) in corneal scrapping, skin biopsy from hairline or saliva, and
- Presence of neutralizing antibodies >100 IU/ml in CSF or serum after 10th day of illness.

Presence of *Negri bodies*—a cytoplasmic inclusion containing clumped viral nucleocapsid in neurons, confirms the diagnosis after death. However, absence of these bodies does not exclude the diagnosis.

D/D of *furious rabies* includes viral encephalitis (loss of sensorium), tetanus (trismus) and hysteria; while *paralytic variety* may be confused with other causes of acute flaccid paralysis, e.g. Guillain-Barré syndrome, poliomyelitis and post-rabies vaccine encephalomyelitis.

Management is non-specific, unrewarding and aims to ally suffering in terminal phase. Important steps include:

a. Isolation in a quiet room, protected from external stimuli, e.g. light, sound, etc. to prevent spasms,
b. Sedatives and muscle relaxants to reduce anxiety/spasm,
c. Parenteral hydration and nutrition, and
d. Cardiorespiratory support, till possible.

Since these cases are potentially infectious (from a week before the onset of symptoms to death), self protection of health staff by gloves, masks, etc. And proper disposal of contaminated fomites and biological fluids is advisable. *However, man-to-man transmission is virtually unknown*.

Prevention of rabies may be divided into:

- ***Primary prevention*** by
  - Avoidance of contact with potentially rabid dogs,
  - Vaccination of pets, and
  - ***Pre-exposure prophylaxis*** (PrEP) of occupation-exposed personals, e.g. animal handlers, veterinarians, forest workers, etc. with two doses of single site IM or two-site ID tissue-culture vaccine (IM 1.0 ml/ID 0.1 ml) on day 0 and 7 are recommended by WHO and IAP. However, total three IM/ID doses are used for pre-exposure prophylaxis in national rabies prophylaxis program, given on day 0, 7, and 21/28.

    PrEP is generally not required in children, though IAP recommends it after discussion with parents, in view of higher risk of exposure in Indian children.
- ***Secondary (post-exposure) prophylaxis*** is the key of survival after potential rabid bite, discussed below.

MANAGEMENT OF DOG BITE

Important steps in the management of a dog bite include: (a) local wound care, (b) evaluation of exposure, (c) passive immunization with anti-rabies immunoglobulin and (d) active immunization.

Step I. Local wound care is essential in all cases presenting soon after bite, to kill the virus by mechanical and virucidal action. Proper wound care reduces risk of rabies by 80% and includes:

- *Cleaning*, i.e. immediate washing of wounds/licks and adjoining area with soap and running-water for at least for 5–10 minutes.
- *Irrigation of deep wounds* with virucidal agents, e.g. povidone iodine or alcohol. Cauterization with carbolic acid is no longer recommended.
- *Avoidance of suturing*, as further trauma increases local vascularity and facilitates spread of virus in deep tissues. If essential, it should be deferred as long as possible and done after local infiltration of Rabies immunoglobulin (RIG).

Step II. Evaluation of exposure: A dog bite is considered as potential risk for rabies if:

- *Bite by* a stray, domestic but unvaccinated, untraceable, or abnormally aggressive dog,
- *Bite was unprovoked*, and
- *Severity of bite* involved actual bite/scratch with skin penetration *or* licks over previous scratch, abrasion, mucous membrane or open wound.

A classification system, depending on the severity of exposure and risk of disease is frequently used to decide the need for post-exposure prophylaxis **(Table 10.45)**.

Step III. Passive immunization aims to prevent immediate attachment of virus to the nerve endings, till vaccine-mediated immunity develops.

Presently, there are two options for passive immunization-human rabies immunoglobulin (HRIG), and

TABLE 10.45: WHO categories for exposure risk and post-exposure ARV prophylaxis

Category	*Type of contact*	*Intervention*		
		Local	*HRIG*	*ARV*
I	Licks on unbroken skin Touching/feeding of animals	Yes	No	No
II	Nibbling of uncovered skin Minor scratches, no bleeding Licks on broken skin	Yes	No	Yes*
III	Single/multiple transdermal bites Contamination of mucus memb with saliva (licks)	Yes	Yes	Yes*

HRIG: Human rabies immunoglobulin; **ARV:** Anti-rabies vaccine
*ARV may be discontinued after 10 days (observation period), if animal remains asymptomatic or killed humanly and found negative for rabies on laboratory workup

monoclonal antibodies, e.g. Rabishield® or Twintab®. Equine rabies immunoglobulin (ERIG) are no longer recommended due to serious side effects.

WHO as well as IAP encourages use of monoclonal antibodies instead of RIG due to easier availability, lower cost, lesser side effects, and possibly greater effectiveness. These antibodies bind ectodomain of G glycoprotein of the virus to block its entry into neighboring cells, both products (Rabishield® or Twintab®) are nearly comparable in efficacy and cost. Rabishield® is available 40 IU/ml, with recommended dose of 3.3 IU/kg, Twinrab® is available as 300 or 600 IU/ml with recommended dose of 40 IU/kg.

Passive immunization, is most effective when given immediately after exposure, but may be given till 7th day of first vaccine dose, by which the active immune response to vaccine is expected to develop. These antibodies must be infiltrated locally at the time of the first vaccine dose or upto 7th day of first dose. If the calculated dose is insufficient to infiltrate all the wounds, it may be diluted in sterile normal saline to get a volume enough to be infiltrated around all the wounds.

Step IV. Active immunization: Two types of anti-rabies vaccines are available in India—(a) *cell-culture vaccines*, e.g. purified chick-embryo vaccine (PCEV), human diploid-cell vaccine (HDCV), purified Vero-cell vaccines (PVRV), and (b) embryonated egg-based vaccines, e.g. *purified duck-embryo vaccine* (PDEV). All are safe, stable and equally effective with >99% protective efficacy. All these vaccines contain minimum 2.5 IU antigen/dose, available in lyophilized form with sterile water as diluents and must be stored at 2–8°C. Side effects are rare and insignificant, e.g. local pain, fever or malaise, though a few cases resembling Guillain-Barré syndrome are reported with HDCV. PCEV should be avoided in children with history of egg-allergy.

Post-exposure prophylaxis (PEP): All vaccines are given as 1.0 ml/dose (0.5 ml for PVRV) over deltoid or anterolateral thigh region as total four doses intramuscularly on *day 0, 3, 7 and 14–28, as recommended by WHO and IAP,* though 5 doses (0, 3, 7, 14 and 28 days) are used in National Rabies Prophylaxis Programme.

Intradermal (ID) vaccination is cost-effective alternative to intramuscular vaccination due to lesser dose requirement (0.1 ml/dose), when large number of vaccines are available simultaneously, as in major public health centers. Government of India provides ID vaccination (under National Rabies Control Programme, given as two ID doses on both deltoids on days 0, 3, 7 and 28). ID vaccination is not recommended for individual practice or in immunocompromised cases.

Re-exposure prophylaxis in previous vaccinated children needs only two IM/ID doses on *day 0 and 3*, if the last dose was received 3 months back. Rabies immunoglobulin is not required in these cases.

10.28 PEDIATRIC HIV INFECTION

Human retroviral infections include two distinct groups: *human T lymphocytic viruses* (HTLV-1 and 2) and *human immunodeficiency viruses* (HIV-1 and 2). HTLV infections have been found associated with leukemia, lymphomas, myelopathy and tropical spastic paraparesis; while HIV infections are responsible for the current AIDS pandemic, discussed here.

Since the first case reports in 1981, HIV/AIDS pandemic has been the major global challenge to recent medicine. In India, first case, a sex worker, was reported from Madras in 1986 while first HIV-infected child was diagnosed in Mumbai in 1987.

Magnitude of problem: While HIV/AIDS pandemic began from North America and Africa, it spread rapidly throughout the world. In recent years, infection is decreasing due to social and therapeutic interventions, though continues to be a major public health problem in India.

Currently ~38 million people are estimated to living with HIV/AIDS (PLHA) globally, including ~23 lakhs in India (NACO 2021) pediatric HIV/AIDS infection in India accounts for <5% of total cases (~76000 children <15 years, NACO 2021) with a declining trend in recent years due to effective perinatal transmission prevention program. *Children living with HIV* (CLHIV) is the new term used instead of HIV infected children.

Virology: Causative virus was isolated by *Luc Montagnier* in France and *Robert Gallo* in USA during 1982–83, but named as Human immunodeficiency virus or HIV in 1986.

Two distinct but structurally related types of HIV virus have been identified in human disease—*HIV-1*, responsible for >90% cases; and *HIV-2*, which is less common (<3%) and associated with less severe disease. Dual infections occur in ~5–7% cases.

Structurally, HIV virus includes a *central cylindrical virion core*, surrounded by two major viral *envelope proteins*—gp120 (outer layer) and gp41 (inner layer). Virion core contains a single strand RNA (viral genome) and various structural proteins encoded on this genome, e.g. p24, reverse transcriptase, integrase, etc.

Modes of transmission: While virus is excreted in various body fluids, it is extremely labile in external environment and adult infection is acquired by direct contact with infected blood during—(a) homo/heterosexual intercourse, (b) blood product transfusions, (c) shared IV needles in drug users, or rarely, (d) occupational exposure in health care workers.

Unlike adults, >95% of HIV infection in children are acquired perinatally (vertical transmission) from infected mothers. Rare horizontal modes of infection in children

TABLE 10.46: Risk factors for perinatal HIV transmission

Maternal factors:
- Severity of infection
  - Symptomatic infection (AIDS)
  - Low CD4 count
  - High viral load
- No anti-retroviral prophylaxis/treatment
- Other less important factors
  - Infection with HIV1 viral type
  - Primary infection during pregnancy
  - Co-existing vitamin A deficiency

Obstetrical factors:
- Postmaturity
- Premature rupture of membranes/chorioamnionitis
- Prolonged labor or interventions, e.g. forceps
- Vaginal delivery

Post-natal factors:
- Breastfeeding
- Maternal breast/nipple problems

include-blood product transfusions, e.g. in thalassemics/hemophiliacs, sexual abuse and very rarely, IV drug abuse in adolescents.

Perinatal transmission: All infected mothers do not transmit infection to their babies with overall risk of ~30–40% in absence of any interventions, depending on many maternal and obstetric factors **(Table 10.46)**. Perinatal mother to child transmission may be acquired as:

- *Peripartum infection* (~60%) during the passage of baby through infected vaginal canal, is the commonest mode of infection, specially in instrumental deliveries.
- *Transplacental infection* (~25%) is rare before 20 weeks of gestation and usually occurs in last trimester due to degenerative placental changes, thus the risk being directly proportional to duration of gestation.
- *Postpartum infection (~15%)* via breastfeeding usually occurs in early stages of breastfeeding, when breast/nipple problems are common. Although ingested virus is usually destroyed in gut, it may enter baby's circulation through oral/intestinal mucosal lacerations, common in newborns.

Pathogenesis of HIV infection revolves around the *special* affinity (tropism) of virus towards human cells bearing CD_4 markers on their surfaces, i.e. (a) immunological cells, e.g. T-lymphocytes, monocytes and macrophages, (b) neuronal cells, e.g. dendritic cells, microglia, astrocytes, etc. and (c) others, e.g. placenta, skin and deeper tissues. Natural history of HIV infection may be divided into four phases:

a. **Primary infection:** Immediately on entry, the virus infects dendritic neuronal cells (in skin), circulatory CD_4 lymphocytes and gut-associated lymphoid tissue, and replicates rapidly, leading to: (a) destruction of the infected cell *(cytopathic effect)*, (b) further infection of other cells and (c) transport of infected cells to regional lymphoid tissues. This phase is associated with significant decline in CD_4 cells with inversion of CD_4/CD_8 ratio.

b. **Initial viremia** after 1–3 weeks with rapid increase in virus infected cells, leads to: (a) dissemination to other tissues, e.g. CNS, (b) rapid fall in CD_4 counts, and (c) reactive lymphoid hyperplasia, clinically presenting as *acute retroviral syndrome* (flu-like illness) for 2–4 weeks. During above two phases, plasma virus may be detected by culture, antigen tests or molecular methods (PCR) but antibody-tests are negative. (*Window period*).

c. **Latent period** due to development of vigorous HIV-specific humoral/cellular immunity after 4–6 weeks of primary infection, which *limits the viral replication but does not eliminate the virus*. During this phase, CD_4 counts recover and viral load is substantially reduced but ELISA test becomes positive. However, substantial viral population survives in lymph nodes and neuronal cells, which act as *sanctuary* for residual infection. In acquired infections of adults, this period may be as long as 10–15 years.

d. **Progressive immunodeficiency** due to slow but continued viral replication within various body cells with CD_4 markers, leads to development of AIDS-indicator illnesses, e.g. opportunistic infections (OIs), HIV encephalopathy, etc. Progression from HIV infection to disease depends on many known and unknown factors, most important being the balance between T-helper (CD_4) and killer/suppressor cell (CD_8) population and ability of the lymph nodes to limit the infection.

Natural course of perinatal infection in children is faster than in adults due to:

- Higher viral load due to sustained exposure in intrauterine, peripartum and postnatal period.
- Large and expanding CD_4 cell-pool in growing baby, facilitating viral multiplication
- Relative immaturity of HIV-specific immune responses, to limit the infection

Consequently, HIV infection in children progresses rapidly, with *shorter latent period* and development of symptomatic disease within few months or years. If not diagnosed and treated, 35% of HIV infected children die by first birthday and 60% by three years.

Clinical presentation of HIV infection in perinatally infected children depends on the age, immune status, presence of co-existing diseases, e.g. malnutrition and tuberculosis and probably, the timing of infection. Four recognized variations in clinical course of perinatal infection are:

- ***Early progressors*** (50–60%), which present in early infancy with severe bacterial illnesses or *Pneumocystis*

carinii pneumonia (PCP) and usually do not survive beyond infancy. These children are probably infected *in utero*, during early gestation.

- ***Intermediate or slow progressors*** (30–40%), which present in late infancy or soon after, with failure to thrive, chronic diarrhea, recurrent infections, encephalopathy and opportunistic infections (OI). These children are probably infected in late gestation or during vaginal delivery.
- ***Long-term survivors or non-progressors*** (5–15%), presenting beyond 3–5 years of age with signs of relatively preserved immunity, e.g. lymphadenopathy, hepatosplenomegaly, lymphocytic interstitial pneumonitis (LIP) and chronic parotitis.
- ***Elite controllers*** (<1%) which are least common but most fortunate children, who remain asymptomatic with undetectable viral load (< 50 copies/ml) without antiretroviral therapy.

Clinically, HIV infection in children may begin as non-specific illnesses with abnormal course or with typical AIDS indicator illness. Some important presentations are as follows:

- **Failure to thrive** is the commonest presentation in Indian children. However, *Wasting syndrome*, seen in adults, is not as common in children and diagnosis requires presence of three features: (a) failure to thrive, (b) chronic diarrhea/enteropathy, and (c) prolonged pyrexia.
- **Respiratory manifestations** are second commonest manifestations, presenting as: (a) recurrent/persistent upper respiratory infections, e.g. sinusitis or otitis media, (b) recurrent/serious lower respiratory infections, e.g. bacterial/PCP pneumonia, or (c) chronic lung disease, e.g. tuberculosis or lymphocytic interstitial pneumonitis (LIP).

  P. carinii (P. Jirovecii) pneumonia (PCP) is the commonest OI in infants and ~70% cases present <1 year of age with acute/sub-acute onset of fever, respiratory distress and progressive hypoxemia. X-ray findings vary from diffuse interstitial infiltrates or ground-glass appearance in early disease to nodular lesions in late stages.

  Lymphocytic interstitial pneumonitis (LIP) is a common chronic lung disease in HIV-infected children, usually without significant immunosuppression. An association with Epstein-Barr virus has been postulated. Most cases present in 3–5 years age group, with insidious cough, dyspnea, wheeze, progressive hypoxemia and digital clubbing (d/d bronchiectasis). Confirmation requires lung biopsy, though chronic lung disease, X-ray findings (diffuse lace-like reticulonodular pattern) and exclusion of tuberculosis point towards the LIP.
- **GIT manifestations** vary from: (a) upper GIT manifestations, e.g. oral/esophageal candidiasis, recurrent herpes stomatitis, (b) lower GIT manifestations, e.g. chronic diarrhea, and (c) accessory manifestations, e.g. chronic parotitis, hepatosplenomegaly and coexisting hepatitis.

  Chronic diarrhea, the commonest GIT manifestation, may be due to: (a) HIV *enteropathy*, i.e. primary HIV infection of gut, (b) common infections, e.g. bacterial, viral, giardia, amebiasis, etc., (c) local gut OIs, e.g. candidiasis, Cryptosporidium, Isospora, etc., and (d) systemic OIs, e.g. CMV, *Mycobacterium avium intracellulare* (MAC), etc. Frequently associated with failure to thrive (*Wasting syndrome*), it may accelerate progression of HIV disease.

  Candidiasis, the commonest OI of GIT, present as persistent oral or esophageal thrush, dysphagia due to esophageal candidiasis, or chronic diarrhea due to intestinal candidiasis.
- **CNS involvement** may be due to p*rimary* HIV encephalopathy or *secondary to OIs, e.g.* bacterial meningitis/abscess, tubercular meningitis, and toxoplasmosis. Unlike adults, cryptococcal meningitis and CNS tumors are less common in HIV-infected children.

  HIV encephalopathy develops in >40% survivors beyond infancy due to direct viral infection and cytopathic damage to neuronal cells and usually presents in 2nd year of life with: (a) regression of milestones/cognitive function, (b) microcephaly, and (c) progressive symmetrical spastic paresis with gait abnormalities. cerebral atrophy and basal ganglia calcification are common on neuroimaging.
- **Skin manifestations** are seen in ~30% cases at some time, and include recurrent impetigo, severe scabies, molluscum contagiosum, herpes simplex or varicella-zoster infections. *Kaposi sarcoma*, a common skin tumor in HIV-infected adults, is extremely rare in children.
- **Hemato-oncological manifestations** include moderate/severe anemia, thrombocytopenic purpura and malignancies, e.g. non-Hodgkin's or CNS lymphomas.
- **Opportunistic infections (OIs)** are hallmark lesions in AIDS, though causative pathogens vary with the severity of immunosuppression and CD_4 counts **(Table 10.47)**. Four commonest OIs in Indian children are severe/recurrent bacterial infections, candidiasis, PCP and tuberculosis.

  Tuberculosis is the commonest co-infection in HIV-infected children, present in ~40–50% cases. Disseminated/extrapulmonary tuberculosis is more common than pulmonary disease. Diagnostic confirmation may be difficult due to false-negativity of tuberculin test in immunocompromised state, non-specific X-ray findings, and usually AFB-negative disease in children. A tuberculin test of >5 mm is considered as positive in HIV-infected children.

TABLE 10.47: Common OIs, according to CD_4 count

CD_4 count	*Common OIs*
>500	Rare
500–200	RBI, TB, Candida[1], HSV[1], VCZ
200–100	PCP, Toxoplasma, Candida[2], HSV[2]
100–50	CMV, Cryptococci
<50	MAC

[1]superficial/mucocutaneous disease [2]invasive disease,
RBI: Recurrent bacterial infections

- **Non-infective systemic lesions** are rare in children and include cardiomyopathy, nephropathy and hepatitis (usually due to co-HBV/HCV infection).

Diagnosis: Possibility of HIV infection should be suspected in children with:

- Known HIV infection or high-risk behavior in parents,
- History of multiple transfusions,
- High-risk for sexual abuse, e.g. street-children, and
- Presence of clinical indicators for HIV disease.

These cases require laboratory screening after appropriate pretest counseling of parents.

While many diagnostic tests are available for HIV infection, the choice differs according to the age of child.

Diagnosis of HIV in children >18 months rests on detection of IgG antibodies against HIV by ELISA/rapid tests as follows:

- Two positive HIV-antibody tests done sequentially using different principles/antigens but using same serum/plasma sample in a symptomatic child, ***or***
- Three positive HIV-antibody tests done sequentially using different principles/antigens but using same serum/plasma sample in an asymptomatic child. Indeterminate results (two positive and one negative test in asymptomatic child) must be tested again on a second sample after 14–28 days.

Currently used rapid tests detect both-HIV1 and HIV-2. Samples, which are reactive for both HIV-1 and HIV-2 or to HIV-2 with only one kit, need confirmation from a reference laboratory.

Other diagnostic tests, e.g. Western blot test, viral cultures and p24 antigen assays are rarely used in practice.

Diagnosis in children <18 months cannot rely on the antibody testing due to transplacental transfer of IgG antibodies from seropositive mother, which may persist till 6–12 months. Diagnosis in these cases rests on detection of total nucleic acid of virus by polymerase chain reaction (PCR-TNA). It is a qualitative test to both DNA and RNA, superior to the previously used DNA-PCR with high sensitivity (99%) and specificity (99%) after 6 weeks of age.

An infant is considered as HIV positive if two PCR tests are positive and HIV Negative if two PCR tests are negative, of which at least one is done after 4–6 months of age.

All perinatally exposed infants, born to a seropositive mother must be tested as per early infant diagnosis (EID) guidelines, recommended by NACO 2021, discussed later.

Presumptive diagnosis is rarely necessary at present due to wide availability of diagnostic facilities. However, in cases where the final confirmation is getting delayed due to some reasons, presumptive diagnosis can be made for the purpose of initiating ART provided: (a) child is HIV-antibody positive ***and*** (b) have *any of two of the following*: (a) oral thrush, (b) severe pneumonia, (c) severe sepsis, or (d) any AIDS indicator illness, e.g. PCP, cryptococcal meningitis, severe wasting, Kaposi sarcoma or extrapulmonary tuberculosis, etc.

Prevention of HIV infection in children largely revolves around prevention of perinatal or parent to child transmission (PPTCT) with four-pronged strategy: (a) Primary prevention to reduce the general HIV prevalence, (b) Prevention of unintended pregnancies, (c) Prevention of mother to child transmission, and (d) care and support to HIV positive mothers.

NACO guidelines 2021 recommends that:

- **Universal HIV testing of pregnant mothers with opt-out option:** *All pregnant women attending antenatal care must be offered HIV counseling and testing, with an opt-out option*, i.e. choice to refuse it. However, those who opt-out of HIV testing must be re-counselled to explore reasons for the same, address any misunderstanding and encourage to reconsider her decision. However, no mother should be tested without her consent.
- **Anti-retroviral therapy to HIV infected mothers:** All HIV-positive pregnant women including those presenting in labour and breastfeeding should be initiated on a triple-drug ART regardless of CD_4 count and clinical stage (Treat all), for preventing mother to child transmission and should continue lifelong ART. Preferred regimen for this purpose is PO *Tenofovir (300 mg) + Lamivudine (300 mg) + Dolutegravir (50 mg), once a day*. While it is important to obtain blood samples for CD4 count and baseline tests before initiating ART, initiation of therapy should not be delayed for want of results.

Rule of 95% includes that: (a) >95% pregnant mothers are registered with at least one antenatal care check-up, (b) >95% of pregnant women are tested for HIV, and (c) >95% of HIV positive pregnant women are on ART.

- **Antiretroviral prophylaxis to HIV-exposed baby,** as discussed later in section of management of a HIV-exposed infant.

TABLE 10.48: Universal safety precautions

Personal protection
- Handwashing with soap and running water
- Use of gloves/gowns and masks during procedures
- Use of long handle wet-mops and gloves by cleaners

Recyclables - disinfection
- *Gloves:* dip in 1% hypo* (20 min) before autoclaving
- *Linen:* Soak in 2–4% hypo* (30 min), before laundry
- *Instruments:* Heat sterilization for min 30 minutes

Waste disposal
- *Sharps:* Dispose in metal container, filled with 1% hypo*
- *Biomed waste:* Dispose in buckets filled with 4% hypo*
- *Spilt blood:* Cover with 4% hypo* (10 min) > mopping

Hypo: Sodium hypochlorite solution

Prevention of HIV infection also involves minimizing the risk of transfusion-related infections by appropriate screening of blood-products and preventing health-care facility exposures by observing universal safety precautions **(Table 10.48)**.

Management of HIV in children, for the sake of discussion, may be broadly divided into:
- Management of a HIV-exposed child
- Management of a HIV-infected child or child with advanced disease

Management of a HIV-exposed child, i.e. child born to a seropositive mother, while still awaiting confirmation of infection in him/herself, involves following components: (1) immediate care at birth, (2) infant feeding, (3) antiretroviral prophylaxis, (4) immunization and vitamin A supplementation, (5) cotrimoxazole prophylaxis, (6) growth and development assessment, (7) early infant diagnosis, and (8) regular follow-up and counseling.

1. **Immediate care at birth:** Care of HIV-exposed infants in delivery room should follow standard neonatal care including the following precautions:
   - Baby's mouth and nostrils should be wiped as soon as the head is delivered.
   - Baby should be handled with gloves until all blood/maternal secretions have been washed off.
   - Cord should be clamped soon after birth, and milking should be avoided. It should be covered with gloved hand and gauze before cutting to avoid blood splattering.
   - Initiate feeding within the first hour of birth according to the preferred and informed choice.
2. **Early infant feeding:** Feeding should be initiated within the first hour of birth in accordance with the preferred and informed choice of the mother.

   As the virus is excreted in breast milk, breastfeeding increases the risk of mother to child transmission by 15–20% and ideal intervention would be not to breastfeed the baby. However, this issue should be viewed in conjunction with potential risks of top feeding, e.g. diarrhea and malnutrition, as well as economical considerations. Risk of HIV transmission via breast milk can be minimized by interventions, e.g. antiretroviral therapy to all seropositive mothers and prophylaxis to their babies. *NACO guidelines 2021* recommend that:
   - All pregnant women should be counselled in antenatal period about advantages and risks of feeding options, i.e. exclusive breastfeeding (EBF) or exclusive replacement feeding (ERF), to assist in informed decision making.
   - EBF is the preferred option for first 6 months and should continue even when complementary feeding is initiated, till nutritionally adequate diet can be provided without breastfeeding and may continue till 24 months as in general population.
   - ERF is an option only if breastfeeding is not possible (maternal death, severe illness, twins) or in cases of individual mother's informed choice. However, AFASS criteria must be fulfilled in ERF cases (***a****cceptable,* ***f****easible, affordable,* ***s****ustainable and* ***s****afe*), in addition to the easy access to health services. Use of bottle for ERF should be strictly avoided due to risk of diarrhea.
   - Mixed feeding increases the risk of transmission and should be avoided at all cost. Top feeds are known to alter gut mucosal barrier, which may facilitate viral entry from breast milk. However, current evidence suggests that in continued presence of maternal ART, mixed feeding is also rendered safe and may be preferred over no breastfeeding at all. Hence, while EBF is still recommended during first 6 months, practicing mixed feeding is not a reason to stop breastfeeding in the presence of ART.
   - If mother plans to return to work, she can be reassured that shorter duration of breastfeeding is still better than never breastfeeding at all.
   - Complementary feeding should be started at 6 months with similar principles as for other children. However, HIV-infected children need additional 10% calories if growing well, 20–30% calories if having poor weight gain and 50–100% calories if having SAM.
3. **Antiretroviral prophylaxis to HIV-exposed baby:** *NACO guidelines 2021* recommends that all infants born to HIV-infected women must receive ART prophylaxis as follows:
   - ***Low-risk infant*** born to mothers with suppressed viral load (<1000 copies/ml) done any time after 32 weeks of gestation, should receive *single drug prophylaxis with Nevirapine* (NVP) for minimum 6 weeks. Syp NVP (10 mg/ml) should be given

a *single oral daily dose* of 15 mg <6 weeks of age (10 mg in infants <2.5 kg), 20 mg in 6 weeks–6 months of age, 30 mg in 6–9 months age and 40 mg above 9 months.

Syrup Zidovudine (ZDV), instead of NVP, is recommended till 6 weeks of age only in setting when NVP will not be effective, i.e. infant born to a mother: (a) with confirmed HIV-2/dual infection, (b) who had received single dose of NVP during earlier pregnancy/delivery, and (c) who is on PI-based ART due to treatment failure. Syp Zidovudine (10 mg/ml) should be given *twice a day* as 5 mg BD (<2000 gm), 10 mg BD (2000–2500 gm) and 15 mg BD (> 2500 gm).

- ***High-risk infants*** (all except as above including mothers not on ART/detected seropositive within 6 weeks of delivery) should receive *dual drug prophylaxis* with NVP and ZDV for minimum 6 weeks, in dose as above (if on exclusive replacement feeding) or 12 weeks (if on exclusive breastfeeding).

4. **Immunization and vitamin A prophylaxis:** HIV-exposed children may be infected or not infected. Even infected children are also unlikely to be severely immunosuppressed in early infancy. While live vaccines are generally contraindicated in immunocompromised states and immune response to may not be optimal in them, HIV-infected children are in fact more susceptible for infections and hence, in higher need of vaccinations. *NACO guidelines 2021* recommends that:

   All HIV-exposed infants should be immunized as per regular schedule, including vitamin A and live vaccines, e.g. BCG, MR and Rotavirus with following exceptions:

   - BCG, if not given at birth and baby has been confirmed as HIV-infected, should be delayed until ART has been started and the infant confirmed to be immunologically stable (CD4 >25%).
   - Measles containing vaccine (MCV) should not be given in HIV-infected children, only in presence of severe immunosuppression. An additional dose of MCV is recommended to HIV-infected children on ART following immune reconstitution (CD4 count >20%). A supplemental dose of MCV may also be considered in HIV-exposed or infected infants >6 months, who are not on ART but at a higher risk of measles.
   - Rotavirus vaccine is recommended to all HIIV-exposed infants, except in those with confirmed HIV infection with severe immunodeficiency.
   - Pneumococcal conjugate vaccine (PCV) should be given at 2, 4 and 6 months with booster at 12–15 months. In addition, HIV infected children >2 years of age should also be given pneumococcal polysaccharide vaccine (PPSV23), at least 8 weeks after the last dose of PCV.
   - Double-dose schedule for HBV is recommended in HIV-infected children due to poor seroconversion, along with frequent assessment of antibody titers and booster, if required.
   - Additional hepatitis A, varicella, influenza and meningococcal vaccines are recommended to HIV infected children, along with human papillomavirus vaccine in adolescents.

5. **Cotrimoxazole prophylaxis:** All HIV-exposed infants should get Cotrimoxazole prophylaxis against PCP with 5 mg/kg/d as single oral dose, starting from the age of 6 weeks till 5 years of age. PO Dapsone 2 mg/kg is the alternative drug in children with serious adverse reactions to Cotrimoxazole or G6PD deficiency. It may be discontinued at 5 years only child is in clinical stage I or 2 and CD count is >350 cells/mm^3 on two occasions, not more than 6 months apart.
6. **Growth and developmental assessment:** All HIV exposed children should be periodically assessed for growth and development as any other child, using standard reference tools.
7. **Early infant diagnosis:** NACO recommends use of PCR-TNA on a dried blood spot (DBS) sample of the infant for diagnosis of HIV-1 infection during infancy, **(Fig. 10.16)** with following considerations:
   - First PCR-TNA should be performed at 6 weeks of age (sensitivity is poor before 6 weeks due to window period). A positive test should be confirmed by repeating the same on a second DBS as soon as possible. However, a negative test should be repeated again at or after 6 months to exclude the infection, after pre-screening the child for HIV antibodies by a rapid test.
   - In a breastfed infant, due to continuing risk of transmission through breast milk, PCR-TNA should be conducted 6 weeks of age and then at 12 weeks after cessation of breastfeeding (or 18 months of age, whichever is later) to exclude the infection.
   - An infant is considered as HIV-positive, if two PCR tests are positive and HIV-negative if two PCR tests are negative, of which at least one is done after 4–6 months of age.
   - All infants, irrespective of the PCR results, should also be tested by ELISA/Rapid test at or after 18 months for confirmation.
   - An infant is considered as seroreverter, if born to a seropositive mother but has been HIV antibody negative by two tests at 6 and 18 months or one test at 18 months, with no other clinical or laboratory evidence of HIV/AIDS.

   Note: In infants >6 months, TNA-PCR is performed only if rapid test is positive as maternal

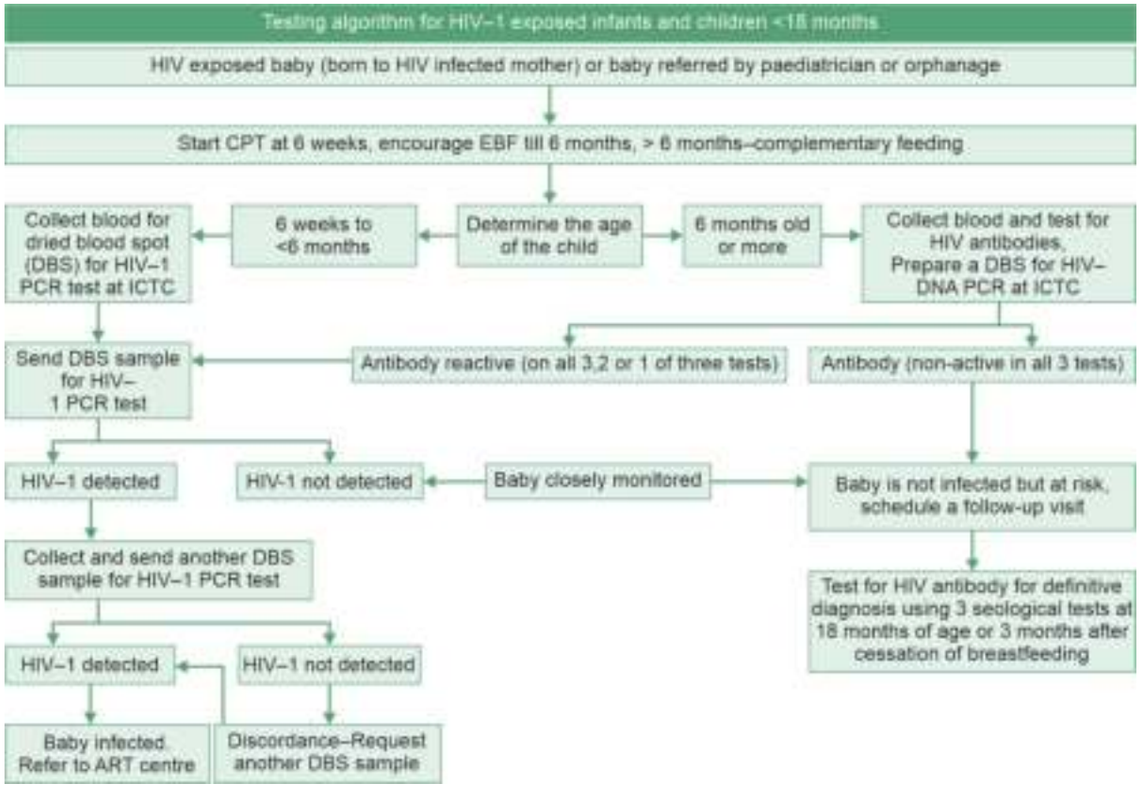

Fig. 10.16: Early infant diagnosis: Testing algorithm for HIV-1 exposed infants < 18 months.

antibodies disappear in 74% and 96% of HIV-uninfected exposed children by 9 and 12 months respectively. In a HIV-exposed child, who is antibody negative at 6 months of age, there are two situations:

- If the infant is not breastfed in the last 3 months, s/he is probably not infected and does not need TNA-PCR testing.
- If the infant continues to receiving breastfeeding, HIV antibody test should be repeated after 3 months of complete cessation of breastfeeding to rule out HIV infection.

All HIV testing should be provided following *five essential Cs*: ***C**onsent, **C**onfidentiality, **C**ounseling, **C**orrect test results and immediate **C**onnection/linkages to services* for HIV prevention, treatment and care.

8. **Follow-up and counseling:** All HIV-exposed infants should be followed up at 6 weeks for collect DBS and initiate Cotrimoxazole prophylaxis and then at 10 and 14 weeks and then at 6, 9, 12 and 18 months for growth monitoring, developmental assessment and nutritional counseling, along with early infant diagnosis, ART/Cotrimoxazole prophylaxis and clinical assessment, as required.

Management of a HIV-infected baby, once the diagnosis is confirmed includes: (a) clinical and immunological staging of the disease, (b) baseline assessment for OIs and primary prophylaxis, (c) initiation of Antiretroviral therapy, and (d) periodic follow-up for adherence and side effects as well as clinical/virological/immunological monitoring for early detection and management of treatment failures, (e) diagnosis and management of concurrent OIs, including secondary prophylaxis, (f) nutrition and feeding, and (g) counseling.

1. **Clinical and immunological staging of the disease:** All HIV-infected children must be assessed clinically in detail, not only for the staging of disease but also for growth and development, nutrition, immunization and presence of co-morbidities, e.g. tuberculosis. Cascade screening of parents and other siblings is also warranted for HIV and other infections.

   Current WHO classification for clinical staging of HIV/AIDS in children <13 years is given in **Table 10.49**.

   All HIV-infected children must be assessed for CD_4 counts to detect and monitor the extent of immunosuppression. According to CD_4 counts, HIV-infected children are categorized into various stages of the immunosuppression **(Table 10.50)**. CD_4 percentage values are preferred in children <5 years than absolute values due to physiologically high cell counts in them.
2. **Baseline assessment to identify presence of OIs and primary prophylaxis:** All HIV infected children should be assessed for presence of OIs, specially tuberculosis on clinical indicators and relevant investigations.

TABLE 10.49: Clinical classification for HIV infection in children <13 years (WHO 2006)

Clinical stage 1 (asymptomatic)
- Asymptomatic
- Persistent generalized lymphadenopathy

Clinical stage 2 (mild)
- Persistent hepatomegaly*
- Papular pruritic eruptions
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Fungal nail infections
- Recurrent oral ulcerations
- Persistent parotid enlargement*
- Linear gingival erythema
- Herpes zoster
- Recurrent/chronic upper respiratory infections (otitis media, otorrhea, sinusitis, tonsilitis)

Clinical stage 3 (advanced)
- Moderate malnutrition* (no response to treatment)
- Persistent diarrhea* (>14 days)
- Persistent fever* (>1 month)
- Persistent oral candidiasis (>8 weeks of age)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis/periodontitis
- Lymph node tuberculosis
- Pulmonary tuberculosis
- Severe recurrent bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis (LIP)
- Chronic lung disease, e.g. bronchiectesis
- Unexplained anemia (<8 gm/dl), neutropenia (<500/mm^3) or chronic thrombocytopenia (50,000/mm^3)

Clinical stage 4 (severe)
- Severe wasting, stunting, malnutrition*
- *Pneumocystis carinii* pneumonia
- Recurrent severe bacterial infections, e.g. empyema, bone/joint infection, meningitis excluding pneumonia
- HSV (orolabial/skin for >1 mo or visceral at any site)
- Extrapulmonary TB
- Kaposi sarcoma
- Esophageal candidiasis (or of trachea, bronchi or lungs)
- CNS toxoplasmosis (>1 mo age)
- HIV encephalopathy
- CMV retinitis or infection of other organs >1 mo age
- Extrapulmonary cryptococcosis (including meningitis)
- Disseminated mycosis, e.g. histoplasmosis
- Chronic cryptospridiosis or Isosporiasis
- Disseminated nontuberculous mycobacterial infection
- Cerebral or B cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- Symptomatic nephropathy or cardiomyopathy

*unexplained

TABLE 10.50: Immunological classification (WHO 2006)

*Categories**	*Age-related CD_4 values*			
	<11 mo	*12–35 mo*	*>36–59 mo*	*>5 year**
Not significant	>35%	>30%	>25%	> 500*
Mild	30–35%	25–30%	20–25%	350–499*
Advanced	25–30%	20–25%	15–20%	200–349*
Severe	<25% or <1500*	<20% or <750*	<15% or <350*	<15% or <200*

*absolute values (cells/mm^3), rest are in %.

Prophylaxis against OIs may be divided into: (i) *primary prophylaxis* before the first attack in high-risk cases, and (ii) *secondary prophylaxis* after the first attack to prevent recurrence.

Primary prophylaxis is indicated with: (a) cotrimoxazole for PCP and toxoplasmosis as discussed earlier, (b) isoniazid (PO 10 mg/kg/day for 6 months) for tuberculosis in all newly diagnosed cases after excluding active disease. In addition, primary prophylaxis is also indicated during the course of disease with (c) Azithromycin (PO 20 mg/kg once a week) for *Mycobacterium avium* intracellular complex when CD_4 count drops <100 cells/mm^3, and (d) Ganciclovir (PO 30 mg/kg TDS) when CD_4 count drops < 50 cells/mm^3.

3. **Antiretroviral therapy (ART):** Life-long highly active ART (HAART) is the cornerstone of management of HIV infected children, while many antiretroviral drugs are available, safety and efficacy of many is not well established in children, as also lack of child-appropriate formulations.

   Depending on the mode of action, commonly used ART drugs in children may be classified as: (a) *nucleoside reverse transcriptase inhibitor* (NRTI), e.g. Zidovudine, Lamivudine, Abacavir, Tenofovir, etc. (b) *non-nucleoside reverse transcriptase inhibitor* (NNRTI), e.g. Nevirapine, Efavirenz, etc. (c) *protease inhibitor* (PI), e.g. Lopinavir, Ritonavir, Nelfinavir, etc. and (d) integrase strand transfer inhibitors (INSTI), e.g. Dolutegravir.

NACO guidelines 2021 recommend following principles for ART in children, as follows:

- ***When to start?*** ART should be initiated in *all children and adolescents living with HIV, regardless of age, CD4 count and WHO staging*. However, initiating ART should be deferred until: (a) acute infections and OIs are treated, if possible, (b) parents have been adequately counselled about the need for adherence and expected side effects.

  In cases associated with confirmed or presumptive tuberculosis, antitubercular therapy (ATT) should be initiated about two weeks before the ART, except in tubercular meningitis when r it should be delayed for 4–8 weeks.
- ***Which drugs to use?*** Standard HAART treatment includes three drugs (*Triple drug therapy*), though choice depends on the age and weight of the child, previous drug exposure, side effects and feasibility. Fixed drug combinations, especially suitable for children, are preferred over to improve adherence. NACO 2021 guidelines recommends that:
  - Children <6 years and Wt <20 kg should be treated with *Abacavir (ABC) + Lamivuduine (LMV) +*

TABLE 10.51: Doses and common side effects of recommended ARTs in children

	Doses (in mg) for different weight bands						
Drug	**<6**	**6–10**	**10–14**	**14–20**	**20–25**	**>25**	***Side-effects***
ABC	120	180	240	300	360	600	Hypersensitivity, ILI
3TC	60	90	120	150	180	300	Rash
LPV/r (4:1)	80 BD	120 BD	160 BD	200 BD	300/200 BD	300 BD	Hepatitis, rash
DTG	5	15	20	25	50	50	Insomnia, Wt gain
TDF	–	–	–	–	–	300	Nephrotoxicity

*All doses once a day, except LPV/r, which is to be given twice a day.
For super boosting, add additional Ritonavir 50 mg < 6 kg and 100 mg above 6 kg

Lopinavir/ritonavir (LPV/r) regimen, in doses as per **Table 10.51**.

- Children aged 6–10 years and Wt 20–30 kg, should be treated with *ABC+ LMV+ Dolutegravir (DTG)*, in doses as per **Table 10.51**.
- Children >10 years and Wt >30 kg should be treated with *Tenofovir (TDF)+ LMV+ DTG*, in doses as per **Table 10.51**.

However, children with HIV-TB co-infection should be provided double-dose DTG (given BD rather than OD) and super-boosted LPV/r (ratio 1:1) with additional dose of Ritonavir, till two weeks after the last dose of rifampicin.

Children/adolescent already initiated on ART in childhood should continue with same regimen with weight adjusted dosing as long as they are virologically suppressed.

- ***How to monitor?*** All cases on ART should be followed up clinically and for relevant laboratory parameters to assess: (a) general well-being including nutritional and development assessment, (b) change in clinical status, e.g. development of new OIs or immune reconstitution inflammatory syndrome (IRIS, discussed later), and (c) adherence to the treatment as well as recognition of side effects.

  CD4 counts should be repeated every 6 months and viral load after 6 months, 12 months and then annually.
- ***When to consider treatment failure?*** Resistance to ART drugs may develop rapidly, but treatment failure should be considered only after fair trial of regimen for minimum 6 months, defined as:
  - *Clinical failure*, with a new/recurrent stage IV event, or progressive developmental deterioration or growth failure;
  - *Immunological failure* with:
    - CD_4 count fall <15% or persists <200 cell/mm^3 in children 1–3 yrs, or
    - CD_4 count falls <10% or persists < 200 cells/mm^3 in children 3–5 yrs, or
    - CD_4 counts fall >50% from peak on treatment level or persist <100 cells/mm^3 or falls to CD4 pre-treatment levels, in older children
  - *Virological failure* with two HIV-1 plasma viral load persistently >1000 copies/ml after 6 months of ART, despite >95% adherence in last 3 months and at least three adherence counseling.

  Children with poor clinical response despite adequate virologic and immunologic responses should be carefully evaluated as all such cases may not represent ART failure. Clinical deterioration after initiation of ART may be due to paradoxical worsening of a known OI, or unmasking of previously undiagnosed OI due to IRIS.
- ***What to change?*** All cases of treatment failure should be managed only at specialized centers, after excluding a complicating OI or drug side effects.

4. **Early detection and management of OIs** is the critical aspect of care in HIV-infected child tuberculosis is the commonest co-infection in Indian HIV-infected children and some base-line information to recognize, diagnose, prevent and treat these OIs have been summarized in **Table 10.52**.
   - ***Cotrimoxazole preventive therapy*** is indicated in all HIV-infected children (as discussed earlier for HIV-exposed children) with 5 mg/kg/d as single oral dose: (a) from 6 months to 5 years of age irrespective of the clinical or immunological staging, (b) from 5 years onwards, if having CD_4 count <350 cell/mm^3 or WHO clinical stage 3 or 4 disease, irrespective of CD_4 count. All cases with history of PCP infection should receive CPT as secondary prophylaxis.
   - ***Life-long secondary prophylaxis*** after first episode/s to prevent recurrence is indicated for: (a) recurrent serious bacterial infections (>2 in a year) with IVIG, (b) PCP with Cotrimoxazole, (c) CMV with Ganciclovir), (d) Toxoplasmosis with Sulfadiazine and pyrimethamine, (e) MAC with Azithromycin and ethambutol, (f) herpes simplex or varicella with Acyclovir.
5. **Nutrition and feeding:** Considering the higher nutritional needs in HIV infected children due to poor nutritional status and impaired immune system with high-risk of infections, WHO recommends that

TABLE 10.52: Common opportunistic infections in HIV infected children

Opp. Infections	*Main presentation*	*Diagnosis*	*Prophylaxis (Indication/drug of choice)*	*Treatment*
Pneumocystis jirovecii (PCP)	Progressive pneumonia with CD4 <200	Bronchoalveolar lavage with special staining	*Primary:* Cotrimoxazole[1] *Secondary:* Cotrimoxazole[1]	Cotrimoxazole[2] + steroids ***Alt:*** *Primaquine + clindamycin*
Bacterial infection	Recurrent/serious infection	Bacterial cultures	*Primary:* Vaccines (sp Hib, PCV) *Secondary:* IVIG[3]	Specific antibiotics
Tuberculosis	Disseminated/ Extrapulmonary disease	Clinical, contact, TT, X-ray Microbial tests	INH PO 10 mg/kg/day x 6 mo (in all cases after excluding active disease)	Specific therapy (*see* Ch 10.13)
Mycobacterium avium intracellulare (MAC)	Disseminated disease with CD4 <50	Blood/marrow/tissue culture	*Primary :* Clarithro/ azithromycin[4] *Secondary:* Clarithro/ azithromycin + ethambutol	Clarithromycin + ethambutol with/without rifabutin or ciproflox[6] ***ALT:*** *Azithromycin[6] + ethambutol*
Candida	Mucocutaneous disease Invasive disease	Clinical appearance Histology/culture	*Primary:* Not recommended *Secondary:* Fluconazole[7]	*OPC:* Clotrimazole *Esophageal:* Fluconazole[8] *Invasive*: Amphotericin B[9]
Cryptococci	Meningitis/Diss. disease	Serology (CSF/serum) India-ink staining (CSF)	*Primary:* Not recommended *Secondary:* Fluconazole[7]	Amphotericin + Flucytosine[10]
Cytomegalovirus disease (CMV)	Ocular: Retinitis CNS: Encephalitis GIT: Esophagitis/colitis	Ophthalomoscopy, CSF serology/MRI Endoscopy/biopsy	*Primary:* ? Ganciclovir [11](CD_4 <50) *Secondary*: Ganciclovir[11]	Ganciclovir[12] ***Alt:*** Foscarnet[12]
Varicella zoster (VCZ)	Recurrent/ multidermatomal Herpes zoster	Clinical, serology	*Primary*: VZIG on exposure *Secondary*: Not recommended	Acyclovir[13] ***Alt:*** Foscarnet[13]
Herpes simplex (HSV)	Recurrent stomatitis, esophagitis, encephalitis	Clinical, serology, viral cultures	*Primary*: Not recommended *Secondary*: Acyclovir[14]	Acyclovir[13] ***Alt:*** Foscarnet[13]
Toxoplasma	Encephalitis Chorioretinitis	Neuroimaging, serology Tissue culture/PCR	*Primary:* Cotrimoxazole[1] *Secondary:* SDZ+PYM+LCV[15]	SDZ+PYM+LCV[16] ***Alt:*** *Clindamycin + PYM+LCV*
Cryptosporidium	Chronic diarrhea	Stool exam	Hygiene	Nitazoxanide[17] or Azithromycin
Isospora	Chronic diarrhea	Stool exam	Hygiene, Cotrimoxazole	Cotrimoxazole[18]
Giardiasis	Recurrent diarrhea	Stool exam	Hygiene	Metronidazole

Alt: Alternative therapy, **OPC:** Oropharyngeal candidiasis, **VZIG:** Varicella-zoster immunoglobulin, **IVIG:** Intravenous immunoglobulin, **Hib:** *H. influenzae* B, **PYM:** Pyrimethamine, **SDZ:** Sulfadiazine, **LCV:** Leucovorin

1. PO Cotrimoxazole 5 mg/kg of (TMP) OD.
2. IV/PO Cotrimoxazole 15–20 mg/kg/d q6hr + IV Dexamethasone 0.3–0.5 mg/kg QID 21 days.
3. IV Immunoglobulin 400 mg/kg/month.
4. PO Clarithromycin 15 mg/kg/d q12hr ***or*** PO Azithromycin 20 mg/kg/week.
5. PO Clarithromycin ***or*** Azithromycin (as above) + PO Ethambutol 15–20 mg/kg/d q24hr ***or*** PO Ciprofloxacin 20–30 mg/kg/d q12–24hr.
6. PO Clarithromycin 7.5–10 mg/kg/d q12hr ***or*** PO Azithromycin 10–12 mg/kg/d q24hr + PO Ethambutol 15–20 mg/kg/d q24hr ***with/without*** PO/IV ciprofloxacin 20–30 mg/kg/d *or* IV/IM Amikacin 5–30 mg/kg/d.
7. PO Fluconazole 3–6 mg/kg OD (in severe recurrent mucocutaneous candidiasis/esophageal candidiasis).
8. IV Fluconazole 3–6 mg/kg OD x 21 days.
9. IV Amphotericin B 0.5–1.5 mg/kg OD × 2–3 weeks after clinical recovery and last positive culture.
10. IV Amphotericin B 0.7–1.5 mg/kg OD + PO Flucytosine 100 mg/kg/d q6hr × 2 weeks followed by IV/PO Fluconazole 10–12 mg/kg/d q12hr × 10 weeks.
11. PO Ganciclovir 30 mg/kg TDS ***or*** IV Ganciclovir 5 mg/kg OD 5 days a week.
12. IV Ganciclovir 5 mg/kg BD × 2–3 weeks. IV Foscarnet 60 mg/kg TDS 14–21 days
13. IV Acyclovir 10 mg/kg TDS × 7–14 days (in severe disease) ***or*** PO Acyclovir 20 mg/kg TDS × 7 days (in mild disease). IV Foscarnet 120 mg/kg/day q8hr × 7 days.
14. PO Acyclovir 80 mg/kg/d q6–8hr.
15. PO Sulphadiazine 80–100 mg/kg/d q6-12hr + PO Pyrimethamine 1 mg/kg OD + Leucovorin (Folinic acid) 5 mg/d alternate day.
16. PO Suphadiazine 25–50 mg/kg QID + Pyrimethamine 2 mg/kg OD × 2 day >1 mg/kg/d + 2–6 mo >1 mg/kg/Alt. day × total 6 mo + Leucovorin 10–25 mg/kg OD.
17. PO Nitazoxanide 100–200 mg BD × 3 days (200 mg BD in children >3 years). PO Azithromycin 5 mg/kg OD × 10 days (10 mg/kg on Day 1)
18. PO Cotrimoxazole 20 mg/kg/d of TMP q6hr × 10 days than q12hr × 3 days.

these children need high-energy, caloric-dense food as follows:
- Caloric requirements should be enhanced by 20–30% in CLHIV with symptomatic HIV or episode of OI, while those with growth faltering may need up to 50–100% additional calories.
- Proteins should supply 12–15% of the energy intake to maintain and/or recover lean body mass.
- Micronutrient supplementation is needed as per RDA.
- Issues related to early infant feeding have been already discussed earlier. Breastfeeding can be continued till 2 years.

6. **Counseling** is a vital component of HIV care and parents should be counselled at all available opportunities for treatment adherence, regular follow-up, timely reporting for opportunistic infections, proper nutrition, etc. Older children and adolescents need age-appropriate disclosure and counseling to ensure treatment adherence.

Immune reconstitution inflammatory syndrome (IRIS) is a collection of signs and symptoms resulting from the ability to mount an immune response to antigens or organisms associated with immune recovery on HAART. It may develop in ~10% cases after starting ART, specially in those with severe immunosuppression.

Clinically, most cases present within 2–12 weeks of initiating ART with unexpected deterioration of clinical status due to unmasking or worsening of sub-clinical co-infections, e.g. tuberculosis, HBV, HCV, MAC and cryptococcal disease.

Diagnosis depends on the high index of suspicion and differentiation from a new OI due to treatment failure may be difficult.

Treatment involves management of unmasked OI. ART should be continued, if possible. Steroids, e.g. prednisolone 0.5–1.0 mg/kg/d × 5–10 days may be used in severe or life-threatening cases to suppress exaggerated inflammatory response. In most cases the symptoms resolve after a few weeks.

10.29 LEPTOSPIROSIS

Leptospirosis (Weil's disease) is an important public health problem in urban India, with localized outbreaks during monsoons. While most cases are asymptomatic, clinical spectrum may range from non-specific febrile illness to severe disease with meningitis or hepato-renal dysfunction.

Epidemiology: *Leptospira interrogans*—the only pathogenic leptospires in humans, is primarily a zoonotic infection, with accidental human infection. *Rat is the main source of human infection,* though other animal reservoirs include dogs, cats and cattle. Infected animals excrete spirochetes in urine, which may be transmitted to humans via exposure to contaminated water or soil.

While sporadic cases are seen in animal-handlers, e.g. agricultural/veterinary workers, localized outbreaks are common in urban slums after heavy rains/floods, due to contact of rat-excreta-contaminated water with human skin.

Pathogenesis: Leptospira enter the body through moist and abraded skin/mucus membrane and spread to all organs via blood stream. Initial spirochetemia is pathologically characterized by vascular endothelial damage and resultant ischemia in liver, kidneys, meningitides and muscles, leading to early manifestations (*septicemic phase*). With appearance of circulating antibodies after 2–7 days, leptospires disappear from circulation but immunological damage may lead to further complications (*immune phase*).

Clinical spectrum: Most cases of human leptospirosis are asymptomatic. In symptomatic cases, the *incubation period is 7–12 days* and clinical presentation may be *biphasic*, divided into:
- *Septicemic phase (3–7 days),* characterized by abrupt onset of high fever with chills, severe headache, conjunctival suffusion, myalgia and nausea/vomiting. On examination, these children have: (a) dehydration with hypotension, (b) extreme muscular tenderness, (c) generalized lymphadenitis and hepatosplenomegaly, and (d) uncommon manifestations, e.g. rash, pneumonia, arthritis, myocarditis, polyserositis, etc.
- *Asymptomatic or silent phase* for few hours or days, though it may be absent in icteric leptospirosis.
- *Immune phase* presenting as either aseptic meningitis (*anicteric leptospirosis*) or hepatorenal dysfunction (*icteric leptospirosis*).

Anicteric leptospirosis is characterized by aseptic meningitis with headache, neurological signs and CSF abnormalities, which resolve spontaneously within a week.

Icteric leptospirosis (Weil's syndrome) is less common in children (<10%) and characterized by—(a) hepatic abnormalities, e.g. progressive jaundice, hepatomegaly and hepatic failure, (b) renal abnormalities, e.g. hematuria or renal failure (c) hypotension/shock and (d) hemorrhagic manifestations, e.g. epistaxis or gut bleeding. Immune phase is relative long (10–30 days) in icteric leptospirosis.

Diagnosis must be suspected in any acute febrile illness with severe myalgia/headache, icterus or renal failure, during rainy season, which may be confirmed by:
- *Elevated IgM antibody titers from 5th day of illness,* >1:100 in at least two specimens *or* >2–4-fold rise over 2 weeks, by standard slide agglutination test or ELISA, with sensitivity of 80–90%,

- *Positive microscopic agglutination test* (MAT) is considered as the gold standard for serodiagnosis, though diagnostic titers vary with endemicity of disease. In regions where leptospirosis is common, there may be a substantial proportion of the population with elevated titers of MAT.
- *Direct identification of leptospires in urine or infected tissues*, by dark-field microscopy, fluorescent antibody staining or phase-contrast microscopy, though sensitivity declines after first week of illness.
- *Molecular tests, i.e. PCR-DNA* in blood, urine or spinal fluid are as diagnostic as direct identification, but cannot identify serovars.

In addition, most cases have thrombocytopenia and must be assessed for liver function tests, renal profile and CSF examination, if clinically indicated.

Modified Faine's criteria may be useful for presumptive diagnosis of leptospirosis awaiting confirmatory reports, based on clinical, epidemiological and laboratory criteria with assigned individual scores.

Treatment is supportive and specific (antibiotics).

- ***Antimicrobial therapy*** is most effective if started within 7 days of onset and drugs of choice include:
  - IV Crystalline Penicillin (50,000 100,000 U/kg/d for 5–7 days) in severe cases with Ceftriaxone (IV 75–100 mg/kg/d for 5–7 days) or Cefotaxime as alternatives, or
  - PO Doxycycline (5–10 mg/kg/d for 7 days) in milder cases. PO Azithromycin (10 mg/kg/d for 3 days) *or* Amoxycillin (50–100 mg/kg/d for 76 days) are alternatives in younger children.
- ***Supportive therapy*** includes antipyretics, cold compresses for muscle pain, correction of fluid and electrolyte abnormalities, continuous monitoring and management of hepatorenal dysfunction, including dialysis.

Prevention of leptospirosis includes: (a) Rodent-control measures, (b) avoidance of contact with contaminated water during floods, (c) prophylactic Doxycycline (200 mg/week) in travelers to outbreak area, and (d) immunization of live-stocks.

10.30 FUNGAL INFECTIONS

Fungal infections may be *superficial*, e.g. oral thrush, skin/nail mycosis, etc. or *invasive*, involving fungemia or systemic tissue disease. While superficial fungal infections are common, invasive disease is rare except in immunocompromised children.

This chapter deals with three important fungal infections—candidiasis, aspergillosis and cryptococcal meningitis. Others, e.g. histoplasmosis (*H.capsulatus*) blastomycosis (*B.dermatitidis*), coccidiomycosis (*C. immitis*), and mucormycosis are extremely rare in Indian children.

Candidiasis is the commonest human fungal infection due to *C. albicans*, though *non-albicans* species are emerging as important pathogens for invasive disease. As candida is a common colonizer of gut, respiratory tract and vaginal flora, the term *candidiasis* usually refers to superficial overgrowth or invasive systemic disease.

High-risk factors: Candidiasis is the commonest opportunistic infection in immunocompromised children and those on prolonged antibiotics, though also seen in normal newborns (as oral thrush or diaper dermatitis) and adolescent females (as vulvovaginitis).

Clinical spectrum of candidiasis depends on the risk factors and usually include:

Oral candidiasis (thrush) is commonest candidal infection, seen in: (a) normal newborns and infants <3 months, (b) prolonged antibiotic therapy, (c) prolonged use of steroid inhalers, and (d) immunocompromised children. *Clinically*, it is characterized by superficial white plaque on oral mucosa, tongue and palate that leaves punctate bleeding on removal (Ch 14.3.3).

Diaper dermatitis presents as confluent popular erythema with red satellite pustules over diaper area. It is common in infants on antibiotics, chronic diarrhea or contact dermatitis.

Systemic (invasive) candidiasis is seen in: (a) extreme preterms/low birth weight newborns, (b) immunocompromised states, and (c) after prolonged vascular/urinary catheterization. Infection form colonized sites may spread directly (esophageal candidiasis, candiduria) or hematogenously, to produce systemic illness, e.g. pneumonia, meningitis and candidemia.

Chronic mucocutaneous candidiasis is a heterogeneous group of *T-cell defects*, characterized by persistent/recurrent mucocutaneous candidiasis, usually associated with endocrinopathies, e.g. Addison's disease and other autoimmune disorders. Invasive disease is rare and treatment is prolonged topical antifungal therapy.

Diagnosis of superficial candidiasis is largely clinical, while invasive disease may be confirmed by: (a) direct demonstration of yeast cells/hyphae from skin/mucosal scrapping, *or* (b) fungal cultures from blood, CSF or urine. In catheter-related cases, removed catheter-tip should always be cultured to confirm the source of infection.

Treatment: Superficial candidiasis is treated with topical anti-fungal preparations, e.g. miconazole, clotrimazole, nystatin or gentian violet, apart from supportive measures, e.g. frequent change of diapers and topical steroid creams, if severe inflammation is present.

IV Liposomal Amphotericin (5 mg/kg/d for 2–3 weeks after last positive culture) is the drug of choice for invasive candidiasis. A second antifungal-Flucytosine or Fluconazole may be added in CNS/renal disease.

Fluconazole is not effective against many non-albicans strains.

Aspergillosis refers to a group of diseases, usually caused by *Aspergillus fumigatus*. Infection is acquired by inhalation of spores (*conidia*), present in soil/decaying plants or rarely by wound contamination.

Risk factors for aspergillosis include: (a) inherent atopic states (*asthma*), (b) heavy/prolonged exposure (*Farmer's lung*), (c) chronic lung disease (allergic bronchopulmonary aspergillosis), and (d) immunocompromised host, e.g. HIV, neutropenia or malignancies (invasive disease).

Clinically, it may present as: (a) non-invasive disease pulmonary or sinus aspergilloma or otomycosis, (b) invasive pneumonia or disseminated aspergillosis, and (c) hypersensitivity syndromes, e.g. asthma, bronchopulmonary aspergillosis, etc.

Diagnosis depends on: (a) clinical suspicion, (b) presence of fungal mycelia/hyphae in tissue lesions or sputum on microscopy/culture, and (c) allergy tests, e.g. skin test, specific IgE levels or radioallergosorbent test (RAST) in hypersensitivity syndromes.

Treatment of choice is: (a) IV/PO voriconazole or liposomal Amphotericin B *in invasive disease*, (b) topical antifungals and steroids in *non-invasive disease*, and (c) steroids for hypersensitivity manifestations; along with supportive therapy. Duration of therapy depends on the site of infection, severity of disease and clinical response.

Cryptococcosis (*C. neoformans*) is the second commonest fungal infection in HIV +ve population, after candidiasis. Infection is acquired by inhalation of spores, present in soil or vegetations contaminated by bird-droppings.

Clinically, sub-acute meningitis is the commonest feature of invasive disease in immunodeficient children, followed by sepsis-like syndrome, lymphonodular disease, cutaneous ulcers/warts and skeletal disease. Cryptococcosis is extremely rare in immunocompetent individuals, except asymptomatic/progressive pneumonia in heavily-exposed adults, e.g. pigeon breeders or bird-traders.

Diagnosis rests on clinical suspicion in immunodeficiency state, supported by latex agglutination test in serum or CSF (titers >1:32). Confirmation requires recovery of fungus on CSF/serum culture or in biopsy tissues.

Treatment of choice for invasive cryptococcosis, (e.g. meningitis) is IV Amphotericin B, with/without Flucytosine till complete response, followed by *life-long maintenance therapy with Fluconazole*. Mild cases limited to lung involvement may be treated with oral Fluconazole.

10.31 CHLAMYDIAL INFECTIONS

Chlamydiae are obligate intracellular bacteria, which are unable to generate their ATP for metabolic activity and hence, depend on host cells for energy. Two species are important in humans—*C. pneumoniae* and *C. trachomatis.*

C. pneumoniae is an emerging cause of community acquired pneumonia in school children. Organisms are present in nasopharynx of a clinical/subclinical human host (reservoir) and transmitted as a droplet infection.

Clinically, it present as atypical pneumonia, with disproportionately less clinical signs than X-ray findings.

Diagnosis depends on serology, i.e. IgM titers >1:16 on immunofluorescence test. Tissue-cultures from nasopharynx, sputum or bronchoalveolar lavage are confirmatory but rarely possible.

Treatment of choice is PO erythromycin/clarithromycin for 10 days *or* azithromycin for 5 days, in usual doses.

C. trachomatis infections in children are almost always caused by its *trachoma biovar*, though another *lymphogranuloma biovar* is responsible for a rare STD in adults, i.e. *lymhphogranuloma venerum*.

Clinical spectrum of *trachoma biovar* in children varies with age and mode of infection and includes:

- Trachoma (Ch 27.1.4),
- Genital infections, and
- Neonatal disease (conjunctivitis or pneumonia) in infected mothers.

Genital infections are acquired as sexually transmitted disease in adolescents or sexually-abused children. These infections may be asymptomatic or present as urethritis or epididymitis in males; and cervicitis, salpingitis or pelvic inflammatory disease in females.

Neonatal infection is acquired during vaginal delivery through infected birth canal, with premature rupture of membranes as a high-risk factor. While nasopharyngeal colonization is common, clinical disease usually presents with—(a) conjunctivitis, during 2nd week of life, and/or (b) atypical pneumonia at 1–3 months of age. Chlamydia is the leading cause of community-acquired neonatal conjunctivitis after control of gonococcal infections.

Diagnosis is mainly clinical, confirmed by demonstration of organisms in nasopharyngeal, ocular or genital smears, either on fluorescent antibody staining (characteristic inclusion bodies) or tissue-culture.

Treatment depends on the site and severity of infection, though PO erythromycin for 1–2 weeks, is the drug of choice in all cases, including newborns and for trachoma. WHO recommends single dose Azithromycin (PO 20 mg/kg) for treatment of Trachoma. Contacts, e.g. sexual partners and mother in neonatal case, should be treated simultaneously.

10.32 MYCOPLASMA INFECTIONS

Two mycoplasmal infections are of interest in human disease – *M. pneumoniae* and Genital mycoplasma, i.e. *M. hominis* and *Ureaplasma urealyticum*.

***M. pneumoniae* (Eaton agent),** the *smallest self-replicating organism,* is the commonest cause of community-acquired pneumonia in schoolchildren.

Epidemiology: Infection is acquired via droplets from infected host, though development of clinical disease depends on age and immune status. Overt illness is unusual before 3–4 years of age, while children with immunocompromised illness or sickle cell disease are at risk for serious disease.

Clinical spectrum: *Primary atypical pneumonia* is the commonest mycoplasmal illness, responsible for >1/3rd cases of community-acquired pneumonia in school children. Other rare manifestation include: (a) upper respiratory illnesses, e.g. pharyngitis, otitis or sinusitis, (b) airway illnesses, e.g. croup, bronchiolitis, and (c) exacerbation of asthma. Mycoplasma infections may also lead to extra-respiratory complications after 2–3 weeks of respiratory illness, due to autoimmune mechanisms, e.g. (a) Steven-Johnson syndrome, (b) neurological disease, e.g. aseptic meningitis, transverse myelitis, Guillain-Barré syndrome, cerebellar ataxia, and (c) autoimmune hemolytic anemia.

Diagnosis usually rests on serology, i.e. elevated cold agglutinin titers (>1:64) *or* positive IgM-ELISA test. Cultures take >1 week for results and molecular diagnostic tests, e.g. PCR are not commercially available.

Treatment of choice is Macrolides, e.g. Clarithromycin (PO 15 mg/kg/day q12hr for 10 days) or Azithromycin (PO 10 mg/kg/day q24hr for 5 days), with nearly 100% success rate. In rare resistant case, tetracyclines or fluoroquinolones may be used.

Genital mycoplasma (*M. hominis* and *U. urealyticum*) are common colonizers of genitourinary tract in post-pubertal adults, rarely transmitted to newborns or children *via* sexual abuse, genital-hand-genital contact, during vaginal delivery or in presence of chorioamnionitis.

Neonatal infection with genital mycoplasma has been attributed to abortions, stillbirths, prematurity and rarely, neonatal respiratory disease.

Adolescent infection may be asymptomatic or presents with non-gonococcal urethritis in males and vaginitis, cervicitis and pelvic inflammatory disease in females.

Diagnosis of pathogenic infection is difficult due to high colonization rate in normal population.

Treatment of choice is single dose Azithromycin, indicated only in symptomatic cases with pure mycoplasma culture.

10.33 MALARIA

Malaria continues to be a major public health problem in India and has acquired new dimensions due to (a) resurgence in previous low-endemic areas, (b) increasing proportion of severe *P. falciparum* cases, and (c) emergence of drug-resistance.

India aims to *eliminate* malaria with 2030, with zero indigenous cases in the entire country, maintain malaria–free status in areas where transmission has been interrupted, and prevent re-introduction of malaria, as also recommended by WHO Global Technical Strategy for Malaria 2016–2030.

Magnitude of malaria in a community is usually measured as *annual parasite incidence* (API), i.e. number of smear-positive cases per year per 1000 population. Recent years have witnessed major changes in malarial epidemiology in India, as follows:

- Significant decline in the incidence of disease with API of 0.12 in 2021 (*vs* 2.12 in 2001).
- Predominance of falciparum (Pf) infection, accounting for ~57% of all malaria cases (2022).
- Wide regional differences, with maximum cases in Chhattisgarh, Odisha, Jharkhand and North-eastern states (2022).
- Alarming rise in drug-resistance Pf cases, specially to Chloroquine (~40%) or Pyrimethamine (~10–20%). Partial chloroquine resistance in vivax (Pv) malaria is also emerging.

Epidemiology: Human malaria is caused by four species of Plasmodium-an obligate intracellular protozoon: *P. vivax* (benign tertian malaria), *P. falciparum* (malignant tertian malaria), *P. malariae* (Quartan malaria) and *P. ovale*. In India, *P. malariae* accounts for <1% cases in Tumkar and Hassan districts of Karnataka, and *P. ovale* is extremely rare. Few cases of malaria due to *P. Knowlesi* have been reported in south-east Asia, but not in India.

Reservoir: Infected humans are the only known reservoir of infection, except probably chimpanzees in tropical Africa. Infected person is communicable only if gametocytes are present in peripheral blood, which appear on 4–5th day in Pv and 10–12th day in Pf, after onset of fever.

Transmission: Mosquito as a vector for malaria transmission was first identified in 1897 by Ronal Ross from Hyderabad, India. Malaria is transmitted by the bites of infected female *anopheline mosquitoes*, except rare cases of *congenital malaria* (transplacental infection), *transfusion malaria* (infected blood/products) or *needle*-infection in drug-users. Six species of female anopheline are known to transmit malaria. In India, maximum transmission occurs by *A. stephensi* (urban slums) or *A. culcifacies* (rural areas) and rarely by *A. minimus* (North-East states). Vector typically breeds on stagnant water, e.g. ponds, cisterns, fountains and overhead tanks.

Host factors: Malaria is common in all age-groups and in males. Since all infected mosquito-bites do not cause clinical disease, host characteristics seem to play important role, as follows:

- *Newborns* are relatively protected, due to presence of high fetal hemoglobin levels (relatively malaria resistant) and transplacental antibodies.
- *Inherent immunity* is present in some people, probably due to: (a) genetic immunity, dependent on HLA type, (b) absence of surface receptors for merozoites on RBC membrane, or (c) presence of hemoglobinopathies, e.g. sickle cell disease, etc., which resist parasitic entry, impede *in vivo* development, or facilitate their removal.
- *Acquired resistance* due to earlier attacks in endemic population. Most severe malaria occurs in non-immune persons, e.g. travelers to endemic regions.

Environmental factors relate to vector population and activity. Malaria is more prevalent in:

- Areas with suitable vector-breeding conditions, e.g. villages and urban slums, heavy rainfall regions, e.g. north-east states, construction sites and man-made breeding sites, e.g. burrow pits, garden pools and irrigation channels (*man-made malaria*).
- Warm-humid climate from July to November, due to increased vector-activity. Malaria is uncommon in hilly regions due to cold weather, unsuitable for mosquito survival.

Life-cycle of parasite completes in two hosts—*asexual phase* in man and *sexual phase in* mosquito **(Fig. 10.17)**.

Asexual phase (in man) begins with infected mosquito bite and entry of *sporozoites* in blood. Most of these sporozoites invade hepatocytes for asexual reproduction, though some are destroyed by phagocytosis in immune people. Asexual phase may be divided into:

a. ***Hepatic (pre-/exo-erythrocytic) phase:*** During incubation period, sporozoites within liver cells develop into *hepatic schizonts*, which eventually rupture to release thousands of *merozoites* (~2000–15,000 in Pv and >40,000 in Pf) in blood. In Pv infection, some schizonts remain dormant in the hepatocytes *(hypnozoites)* to mature and rupture later, leading to late relapses (*exo-erythrocytic phase*). This phase is absent in Pf infections and congenital/transfusion malaria *(no relapse)*.

b. ***Erythrocytic phase:*** Liberated merozoites from liver invade RBCs by attaching themselves on cell-surface receptors and develop intracellularly through many developmental stages, e.g. *ring stage* > *trophozoites* > *erythrocytic schizonts* and again as *merozoites*. Infected RBC ruptures to release them in peripheral blood, with reappearance of fever. Subsequent course of merozoites is:
   - Re-infection of other RBCs and re-cycling till development of adequate natural immunity. Each erythrocytic cycle takes ~42 hrs (~72 hrs in *P. malariae*), responsible for typical periodicity of fever, i.e. tertian malaria (Pv, Pf) or quartan malaria (*P. malariae*).
   - Re-entry of some merozoites (except in Pf) into hepatocytes to re-start hepatic/exo-erthrocytic phase, responsible for relapses.
   - Development into sexual forms, i.e. micro (male) or macro (female) gametocytes, for infection of other mosquitos.

Sexual phase (in mosquito) involves fusion of male and female gametocytes to form zygote in the stomach of mosquito that develops further as *sporozoites* and enters into salivary glands, ready to inoculate next human host.

Pathogenesis: Clinical differences in the severity of illness in Pv and Pf infection mainly relate to *magnitude of parasitemia*, i.e. number of RBCs infested. As many as 30–40% of RBCs may be simultaneously infected in severe Pf malaria, as compared to <5% parasitization in Pv infections. Further, Pv invades only the younger RBCs, while Pf also infects senescent erythrocytes.

Important factors in pathogenesis of malaria are:

- *Hemolysis* of parasitized RBCs, leading to febrile episodes and anemia;
- *Increased cytoadherence* of parasitized RBCs, leading to intravascular clogging and hypoxic-ischemic tissue injury. Falciparum infested erythrocytes tends to adhere to uninfected RBCs (rosetting) to promote cytoadherence, specially in severe cerebral malaria.
- *Immunological injury* with hypergammaglobulinemia, immune-complex formation and release of pro-inflammatory cytokines, (e.g. interleukins and TNF-α), which precipitate or aggravate tissue hypoxia/injury.

Immune response to malaria is slow, incomplete and not life-long, due to antigenic diversity of the parasite. However, repeated exposures tend to reduce the severity of disease due to partial immunity in older population of endemic regions.

Clinical manifestations of malaria begin after an *incubation period* of ~ 9–14 days in Pf and ~ 12–17 days in Pv infection; and depend on the magnitude of parasitized RBCs as well as immune status of host. In endemic regions, e.g. India, even 20–30% parasitemia may be asymptomatic in older cases due to acquire immunity after repeated exposures. Some important manifestations of malaria are as follows:

Classical malaria, is characterized by typical periodicity of intermittent fever. Each episode evolves through following three stages:

a. *Cold stage*, i.e. sudden chills and rigors for ~ 10–15 minutes, followed by,

b. *Hot stage*, i.e. sudden rise of temperature, lasting for 2–3 hours, followed by,

c. *Wet stage*, i.e. profuse sweating, when fever comes down by lysis.

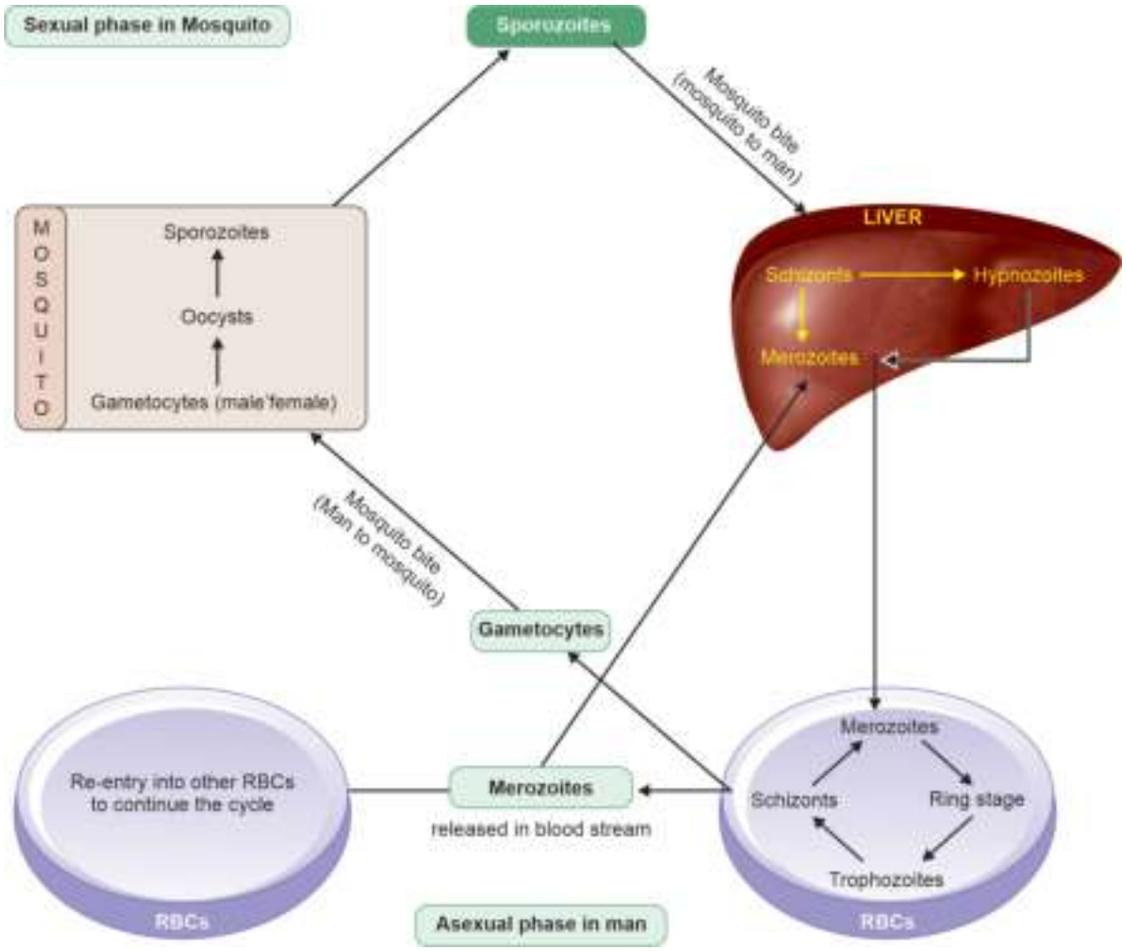

Fig. 10.17: **Life cycle of malaria parasite.**

On examination, mild splenomegaly and pallor is common.

Severe malaria is more common in non-immune population, almost always caused by Pf infection and defined as presence of any of the manifestations enumerated in **Table 10.53**. *Cerebral malaria* is the commonest and most serious presentation of severe malaria in children (Ch 18.11.4). Severe malaria due to vivax malaria is rare, but has been reported. Diagnostic criteria for severe Pv malaria are similar to those for severe Pf malaria, but with no definite parasite thresholds.

Chronic malaria is a common problem in endemic region due to relapses (in Pv infection) or recurrent infections. Armed with partial immunity, these cases often presents with intermittent bouts of mild febrile episodes but *progressive splenomegaly*.

Neonatal malaria is uncommon due to high fetal hemoglobin (relatively resistant), and may be (a) *Congenital* or transplacental, due to maternal infection in last week of gestation, or (b) *Acquired* due to mosquito bite in early neonatal period.

TABLE 10.53: WHO criteria for severe falciparum malaria (2023 update)

- Impaired consciousness (Blantyre coma score <3)
- Generalized prostration (inability to sit/stand/walk)
- Hypoglycemia (Blood sugar < 40 mg/dl)
- Recurrent seizures (≥3 in 24 hours)
- Metabolic acidosis (HCO_3 <15 or lactate >5 mmol/L)
- Severe anemia with PC >10000/µl (Hb ≤5 or Hct ≤15)
- Recurrent or prolonged bleeding
- Jaundice with PC >100000/µl (bilirubin >3 mg/dl)
- Hyperparasitemia (>10%)
- Pulmonary edema (On X-ray or SaO_2 <92%)
- Circulatory shock (SBP <70 mm Hg or CRT ≥3 sec.)
- Renal failure (S. creatinine >3 mg/dl)

PC: Parasite count, **RD:** Respiratory distress, **CRT:** Capillary refill time, **SBP:** Systolic blood pressure

These cases presents with septicemia-like manifestations, e.g. poor feeding, sluggish activity, pallor, jaundice, diarrhea/vomiting and hepatosplenomegaly. Antenatal maternal infection is also associated with intrauterine fetal death, premature labor and IUGR. Although d/d with acquired neonatal malaria is difficult,

congenital malaria is characterized by: (a) onset within 7 days of life, (b) absence of exo-erythrocytic phase with no relapses and (c) positive maternal/placental blood smear.

Diagnosis of malaria depends on the peripheral smear or a rapid diagnostic test, though collaborative hematological findings may support the diagnosis in a clinically suspected case.

- **Peripheral smear (PS):** Demonstration of ring or trophozoite stage on PS is the gold standard for diagnosis of malaria, though possible in only 50–60% cases. Smear yield is higher if—(a) PS is made during acute febrile episode and before anti-malarial therapy, (b) it is prepared from bone-marrow or splenic-aspirate, (c) special staining techniques are used, and (d) multiple smears are examined. Single negative smear does not exclude malaria. *Thick and thin smear* is most commonly used laboratory tool for demonstration of various stages of parasite **(Fig. 10.18)** that involves preparation of two smears: (a) a *thick smear* that increases chances of parasite detection due to more RBC mass, and (b) a *thin smear* to identify the species (Pv or Pf). Commonly used staining procedures include Field's stain, JSB stain and Giemsa stain **(Table 10.54)**.

  The term *parasite index* denotes percentage of parasite-laden erythrocytes, used as a marker of the disease-severity as well as therapeutic response.
- **Rapid diagnostic tests (RDTs),** based on the detection of circulating parasite antigens, are useful to detect malarial infection when microscopy is not possible or delayed. However, these tests should not be used as replacement for microscopy. Among the available RDTs, some can detect only the Pf species (monovalent) while others can also identify Pv or other species (bivalent). Two commonly used RDTs are as follows:

  Parasight-F test is a monovalent RDT, which detects histamine-rich protein (HRP-2) antigen of asexual Pf, with sensitivity of >90% in cases with parasite load of >100–500/µl. However, it may be false-negative in very low parasitemia and false-positive in post-treatment cases as HRP-2 antigen may persist for up to 4 weeks after parasite clearance on treatment. This test cannot detect Pv infection.

  Optimal test is a bivalent RDT that detects parasitic LDH enzyme, produced by all species. Sensitivity and specificity of optimal test is >95% in diagnosis of Pf as well as Pv malaria. It is capable to detect parasite load of as less as 50–100 parasites/µl and becomes negative after successful treatment.

  Sensitivity of RDT depends on the quality and storage conditions of the kit, species and load of the parasite and technique and care used during testing. RDTs may be used as a screening test, though a

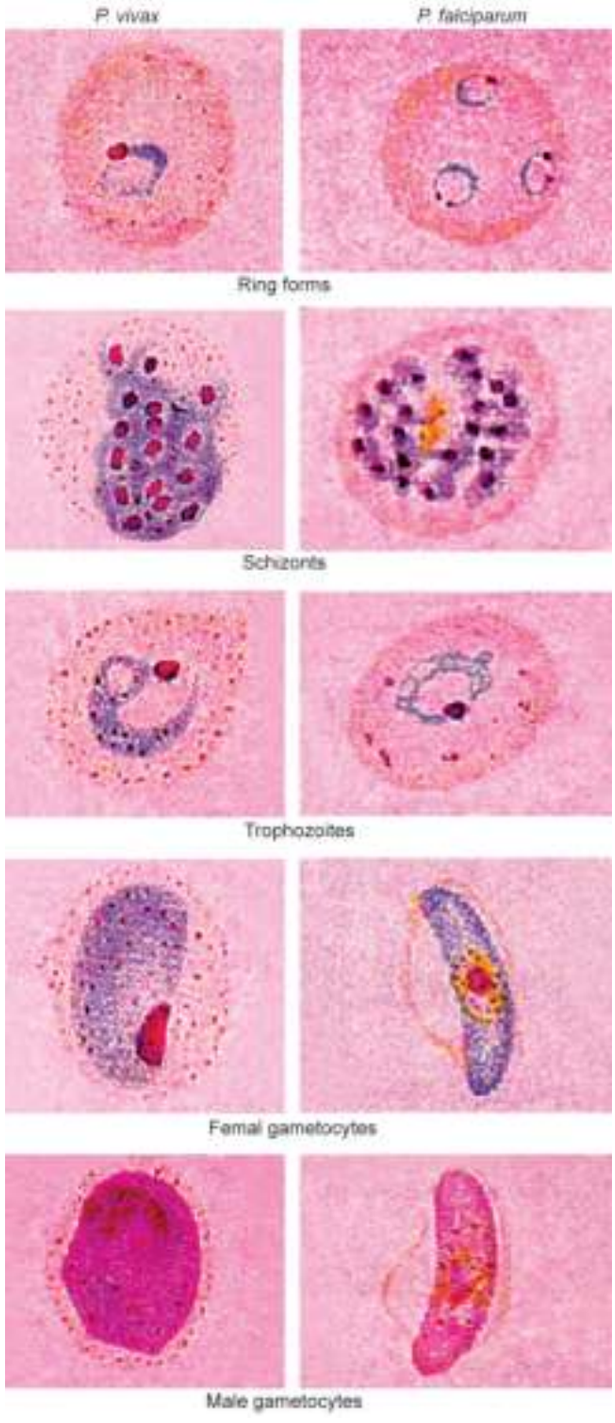

Fig. 10.18: **Peripheral smear in malaria—parasitic stages.**

TABLE 10.54: Staining methods for PS-MP

Leishman's staining:
- Cover the smear with Leishman stain (1–2 min)
- Pour equal volume of buffer water (7–10 min)
- Wash with water and dry

Giemsa staining:
- Fix the smear with acetone-free methanol (1min)
- Cover with giemsa's stain (20 min)
- Wash with water and dry

negative RDT in a strongly suspected case should always be confirmed by microscopy. RDT may not differentiate between active infection and recent effectively treated infections and should not be used to monitor the response to therapy.

- **Other diagnostic tests** of limited utility, include-special staining techniques, antibody detection tests and molecular diagnostic tests. *QBC test or Acridine-Orange staining* involves fluorescent staining of parasitic nucleic acids. It is useful to detect very low parasitemia (~2–3/µl), but species identification is difficult. *Antibody detection tests* are of little clinical significance in endemic regions due to past infection and molecular tests are confirmatory but not freely available. Other laboratory abnormalities, though not diagnostic, help in early detection of *severe malaria* and include severe anemia, thrombocytopenia and hypoglycemia.

Table 10.55 provides an overview of main epidemiological, clinical and laboratory differences between Pv and Pf malaria.

Management of malaria aims to: (a) cure the disease, (b) prevent relapses, (c) render the patient non-infective, and (d) prevent the infection. It includes specific antimalarial therapy as well as supportive measures, e.g. antipyretics, fluid-electrolyte correction, adequate nutrition and treatment of complications.

TABLE 10.55: *P. vivax vs P. falciparum* malaria

	P. vivax	***P. falciparum***
Life cycle		
No. of Merozoites[1]	<15,000	>40,000
Affected RBCs	Young	Any
Parasite index	<5%	>10–30%
EE phase[2]	Present	***Absent***
Gametocytes[3]	4–5th day	10–2th day
Clinical features		
Fever periodicity	48 hours	Usually absent
Complications	Uncommon	***Severe malaria***
Relapse	No	Yes
Smear findings		
RBC size	Enlarged	Normal
RBC stippling	Schuffner's dots[4]	Maurer's spots[5]
Ring stage/RBC	Large, 1–2 rings	Small, multiple
Schizont	Large, ameboid	Small, compact
Pigment	Golden haze	Dark brown
Gametocytes	Spherical	Cresent-shape
Response to treatment		
Drug resistance	Rare	***Common***

[1]Number of merozoites released from hepatic phase; [2]exoerthrocytic phase; [3]day of gametocyte appearance; [4]small, numerous, red dots; [5]large, <20, red dots.

No single anti-malarial agent is effective against all stages of parasite. Currently available drugs may be divided into three groups:

a. *Drugs acting on hepatic phase,* which destroy the sporozoites, prevent hepatic schizogony or prevent erythrocyte invasion by merozoites, e.g. *pyrimethamine, primaquine, proguanil.* These drugs are used to prevent the disease after exposure, i.e. *chemoprophylaxis or* to prevent relapses, i.e. *radical cure* in Pv malaria.
b. *Drugs acting on erythrocytic phase,* which inhibit erythrocytic schizogony and rupture of infected RBCs. These drugs, e.g. *chloroquine, quinine, mefloquine* merely suppress the Pv infection due to limited action on exo-erythrocytic phase; but are curative for Pf infection with no exo-erythrocytic phase. A combination of drugs effective against both erythrocytic and hepatic phase must be used for complete *clinical* as well as *radical cure* in Pv malaria, e.g. chloroquine with primaquine.
c. *Gametocidal drugs,* which destroy gametes to prevent further transmission in new vectors, e.g. *primaquine, mefloquine*, etc. Chloroquine is not gametocidal.
d. *Sporonticidal drugs* prevent maturation of parasite within the mosquito to break transmission cycle, e.g. *pyrimethamine, proguanil*, etc.
e. *Broad-spectrum antimalarial drugs*, e.g. artemisinin derivatives, effective against all forms of erythrocytic stages and gametocytes (except mature forms). However, these drugs are ineffective against extra-erythrocytic forms, sporozoites and merozoites.

Artemisinin combination therapy (ACT) has revolutionized the treatment of falciparum malaria. It involves simultaneous use of two or more schizonticidal drugs with different mode of action. One of the partners in this combination should be an artemisinin derivative due to its high killing rate (reduces parasite load 10,000 fold *versus* 100–1000 fold per cycle with other drugs), lack of serious side effects, low level of resistance and rapid elimination of the drug, which ensures that the parasites are not exposed to sub-therapeutic levels. When combined with slowly-eliminated antimalarials, e.g. lumefantrine or sulfadoxinepyrimethamine (SP), artemisinin derivatives also protect against emergence of drug resistance by drastically reducing the number of parasites exposed to these long-acting drugs.

Five ACT combinations are approved by WHO for use in children-Artesunate+Sulfadoxine-Pyrimethamine (ASP), Artesunate+Amodiaquine (AA), Artesunate+mefloquine (AM), Artemether+Lumefantrine (AL) and Dihydro-artemisinin+Piperaquine (DHP).

WHO 2023 and National Vector Borne Diseases Control Programme (NVBDC) guidelines recommends that all fever cases with suspected malaria should be investigated for confirmation, preferably with microscopy or by RDT, before initiation of the treatment. Specific chemotherapy

in malaria depends on the species of parasite, prevalent pattern of drug-resistance as well as clinical status of patient and may be broadly divided into management of—(a) uncomplicated attack, (b) drug-resistant malaria, and (c) severe malaria.

a. *Treatment of uncomplicated vivax malaria:* Chloroquine continues to be the drug of choice in all cases of uncomplicated Pv malaria, followed Primaquine for 14 days to eliminate the exo-erythrocytic phase for *radical cure* **(Table 10.56)**.

   WHO 2023 recommends Chloroquine in 3 dose-schedule (PO 10 mg/kg stat, 10 mg/kg after 24 hrs and 5 mg/kg after 48 hrs), preferable to the conventional four-dose schedule (PO 10 mg/kg stat than 5 mg/kg at 6, 24 and 48 hrs), though total dose is same, i.e. 25 mg/kg. Dose should be repeated if patient vomits within 30 minutes.

   In regions with chloroquine-resistant Pv, ACT containing Lumefantrine, mefloquine or Piperaquine (AL, AP or AM) is recommended for uncomplicated Pv malaria (WHO 2023).

   Primaquine is contraindicated in infants, pregnancy, lactation and G6PD deficiency. G6PD estimation is advisable in all cases before primaquine therapy, if possible. While 14-day Primaquine therapy is recommended for radical cure, WHO 2023 also recommends additional option of PO Primaquine 0.5 mg/kg/day for 7 days for better compliance of shorter regimen.

   G6PD deficient children may be given 0.75 mg/kg of Primaquine once a week for 6 weeks instead of usual daily dose for 14 days.

b. *Treatment of uncomplicated falciparum malaria:* Considering the high frequency of Chloroquine and Pyrimethamine resistance in India, *ACT* is the treatment of choice for uncomplicated Pf malaria.

   Of these, only two-*ASP* (for states other than north-eastern states) and *AL* (for north-eastern states) are recommended in National Drug Policy for malaria **(Table 10.56)**.

   ASP is not recommended in north-eastern states due to high incidence of Pyrimethamine resistance, in newborns due to risk of competitive bilirubin displacement by SP leading to hyperbilirubinemia, and in HIV-infected children on Cotrimoxazole prophylaxis.

   Author's note: *Author prefers AL over ASP due to: (a) lack of liquid ASP formulations, and (b) risk of missing SP in ASP combinations, as it is provided as separate tablet.*

   In all cases of Pf malaria, ACT should be followed by single dose of Primaquine (0.75 mg/kg) to destroy the gametocyte and break the transmission cycle, except in infants <6 months. G6PD testing is not required (WHO 2023).

c. *Treatment of mixed malaria* is similar to that for pf malaria, except that primaquine has to be given as PO 0.25 mg/kg/day for 14 days, as for Pv malaria **(Table 10.56)**.

d. *Treatment of severe malaria* is life-threatening and specific ant-malarial therapy in all cases including infants, should begin parenterally with any of the three drugs – artesunate, artemether or quinine for *at least first 24 hours, followed by switch-over to oral therapy as early as possible* **(Table 10.57)**.

While National Drug Policy lists Quinine, Artesunate and Artemether in the order of treatment of severe malaria, WHO 2023 recommendations favour Artesunate as the preferred choice, since it takes ~4 hours to achieve adequate quinine levels even after the loading dose. If artesunate is not available, artemether should be used in preference to quinine for severe malaria.

Children weighing <20 kg should receive a higher dose of artesunate (3 mg/kg per dose) than larger

TABLE 10.56: Treatment of uncomplicated malaria

***P. VIVAX* MALARIA**	
PO Chloroquine*	10 mg/kg on day 1 and 2, then 5 mg/kg on day 3 followed by
PO Primaquine	0.25 mg/kg × 14 days
***P. FALCIPARUM* MALARIA**	
In Rest of India (Other than NE states)	
PO Artesunate	4 mg/kg/d × 3 days and
PO PYM+SLF**	1.25 mg/kg on Day 1,
With PO Primaquine	0.75 mg/kg on Day 2
In North-eastern states:	
PO Artemether + Lumifantrine combination	
5–14 kg : 20 + 120 mg BD × 3 days	
15–24 kg : 40 + 240 mg BD × 3 days	
25–34 kg: 60 + 360 mg BD × 3 days	
>34 kg: 80 + 480 mg BD × 3 days	
With PO Primaquine	0.75 mg/kg on Day 2
MIXED MALARIA	
Same as for Pf malaria with	
PO Primaquine	0.25 mg/kg × 14 days

**Pyrimethamine + sulfadoxine, not to be used <5 months

TABLE 10.57: Treatment of severe malaria (Any one)

Quinine[1, 2]	IV 20 mg/kg (Loading), **then...**
	IV/PO 10 mg/kg 8-hrly × 7 days, **with**
	PO Doxycycline 100 mg OD × 7 days (>8 yr) **or**
	PO Clindamycin 20 mg/kg q12hr × 7 days (<8 yr)
Artesunate[3]	IV 2.4 mg/kg (at 0, 12 and 24 hours) **then...**
	IV 2.4 mg/kg OD till PO treatment is possible, **then...**
	PO area-specific ACT, full course
Artemether[4]	IM 3.2 mg/kg (Loading), **then...**
	IV 1.6 mg/kg OD till PO treatment is possible, **then...**
	PO area-specific ACT, full course

[1] Diluted in 5% DW (2 mg/ml) and infused slowly over 2–4 hours.
[2] No loading dose, if received quinine in preceding 12 hours.
[3] Dilute with 3–5 ml of 5% DW and given as bolus.
[4] IM Artemether is given as deep IM and not IV.

children and adults (2.4 mg/kg per dose) to ensure equivalent exposure to the drug.

Following initial parenteral therapy, PO Doxycycline (3.5 mg/kg OD in children >8 yrs) or PO Clindamycin (10 mg/kg BD in younger children < 8 yrs) for 7 days must be added to prevent development of resistance. However, WHO 2023 recommends switch-over to oral ACT for 3 days due to poor adherence for 7-day treatment regimens using doxycycline or clindamycin.

Intensive care with supportive therapy is also essential in these cases, including:

- Restoration of fluid and electrolyte balance, with early correction of metabolic acidosis. However, over-hydration must be avoided to prevent pulmonary edema.
- Regular monitoring of blood sugar for early detection and treatment of hypoglycemia.
- Correction of anemia with transfusions or preferably partial exchange transfusion, which also helps to reduce parasite load.
- Control of seizures with anticonvulsants, e.g. phenobarbitone or diazepam.
- Organ-specific supportive management, as required.
- Treatment of cerebral malaria, the commonest form of severe malaria is discussed in Ch 18.12.6.

Treatment failure in malaria is defined as failure of the fever and/or parasitemia to resolve or recur after treatment within 28 days, further classified as e*arly treatment failure* (no response in 3 days) or *late treatment failure* (4–28 days). Absence of parasitemia on day 28 is considered as adequate clinical and parasitological response (ACPR). All cases of treatment failure are not due to drug resistance and many may represent recrudescence or relapse due to inadequate treatment or re-infection.

Management of these cases, as per current WHO recommendation (2023) is as follows:

- Recurrence of fever or parasitemia within 28 days is more likely due to recrudescence of infection and must be treated second-line treatment, i.e. an alternative ACT known to be effective in the region.
- Recurrence of fever and parasitaemia after 28 days of treatment may be due to either recrudescence, relapse or re-infection. Distinction can be made only by PCR genotyping of parasites from the initial and the recurrent infections. Since PCR is not routinely used in patient management, all presumed treatment failures after 4 weeks of initial treatment should be considered new infections and treated with the first-line ACT. However, reuse of mefloquine within 60 days of first treatment is not recommended due to increased risk for neuropsychiatric reactions.

Prevention: Malaria control strategies in India have been revised periodically, to meet the changing epidemiology, occurrence of outbreaks, drug-resistance and insecticide resistance in vectors.

Malaria vaccines: More than thirty vaccines against Pf malaria are at pre-clinical and clinical stages of evaluation, acting on different stages of the parasite. However, RTS, S (Mosquirix®) is the only vaccine licensed on pilot basis in three sub-Saharan African countries – Ghana, Kenya and Malawi, and has shown significant reduction in prevalence as well as severity of falciparum malaria (Ch 9.2.4). An indigenous malaria vaccine, developed by Serum Institute of India, Pune has also been approved recently and, is expected to available soon.

National Vector Borne Diseases Control Programme (Malaria)

Malaria control strategies in India date back to 1953 with launching of National Malaria Control Programme, which has been subsequently modified many times, presently being the part of National Vector-borne Disease Control Programme (NVBDCP), since 2002. Important components of this program are as follows:

a. **Early diagnosis and management** of malaria cases to reduce the reservoir by:
   - *Passive surveillance*, i.e. examination of peripheral smear in all febrile cases, covering at least 10% of total population, annually.
   - *Standardized protocols for diagnosis*, including use of rapid diagnostic tests in areas where microscopy facility is not available.
   - *Standardized protocols for treatment*, including use of artemisinin-combination therapy in falciparum malaria due to high frequency of chloroquine-resistance.
   - Radical treatment of confirmed vivax malaria for 14 days.
   - *Presumptive anti-malarial therapy* is no longer recommended except in cases from endemic regions with high suspicion of malaria, provided microscopy result is not available within 24 hours and bivalent RDT is not possible. In such cases, full 3-days course of chloroquine is recommended without Primaquine, which should be used only in confirmed cases. Treatment must be modified after smear or RDT results.

b. **Chemoprophylaxis** is indicated only selective groups, e.g. military personals, travelling to high *Pf* endemic areas, along with other personal protection measures, e.g. insecticide-treated nets.
   - *Short-term chemoprophylaxis* (<6 weeks) involves PO Doxycycline 1.5 mg/kg OD from 2 days before to 4 weeks after the exposure. It is contraindicated in children <8 years or pregnant women.

  - *Longer chemoprophylaxis* (>6 weeks) is advised only in adults (not children) with PO Mefloquine 250 mg/week from 2 days before to 4 weeks after the exposure. It is contraindicated in individuals with history of convulsions, neuropsychiatric problems and cardiac conditions.

c. **Vector control** to reduce the transmission, by:
  - *Anti-adult mosquito measures*, e.g. residual spraying/fogging, with DDT, malathion, fenitrothion, etc.
  - *Anti-larval measures*, e.g. source reduction (reducing breeding sites), use of chemical larvicidals (oil, temphos) or biological agents, e.g. fishes.
  - *Personal protection measures*, e.g. nets, repellents, etc.

d. **Information, education and communication** (IEC) campaign is intensified during pre-monsoon season, i.e. June (declared as anti-malaria month).

e. **Ancillary activities,** e.g. research, training, etc.

National Framework of Malaria Elimination (2016-2030)

In line with the WHO Global Technical Strategy for Malaria 2016–2030, National Framework for Malaria Elimination 2016-2030 outlines India's strategy for elimination of the disease by 2030 with well-defined goals, strategies, targets and timelines. It aims to: (a) eliminate malaria (zero indigenous cases) throughout the entire country by 2030, (b) maintain malaria–free status in areas where malaria transmission has been interrupted, and (c) prevent re-introduction of malaria.

10.34 KALA-AZAR

Leishmaniasis denotes varied presentations of infection with multiple species of an intracellular parasite—*Leishmania;* while the term *kala-azar* refers to typical manifestations of *visceral leishmaniasis*, i.e. prolonged pyrexia, gross splenomegaly, anemia, dark pigmentation of skin and failure to thrive.

In India, leishmaniasis is still seen in four states: Bihar, Uttar Pradesh, Jharkhand and West Bengal, though number of cases have declined by over 98% in last decade and India aims to eliminate Kala-azar by 2023.

Epidemiology: Indian kala-azar is mainly caused by *L. donovani*, which is dimorphic in life cycle—aflagellate *promastigote form* in the vector and an aflagellate *amastigote form* in macrophages of human host.

Reservoir of infection is an infected human host, harboring amastigote forms within reticuloendothelial system and, intermittently in peripheral smear.

Mode of transmission is vector-borne, by a female sandfly—*phlebotomus,* which breeds in the hot-humid climate and gets infected after biting infected humans. In the vector, parasite assumes a promastigote form (*leptomonads*) to proliferate in gut and then ascends to pharynx during next 6–9 days (*extrinsic incubation period*).

Pathogenesis: After infected bite, parasite enters into macrophages to transform in amastigote form (Leishmania bodies or LD bodies) and replicates intracellularly. These infected macrophages eventually concentrate in spleen, liver and bone marrow, leading to *hyperplasia of reticuloendothelial system*-pathological hallmark of disease. Rarely, congenital and blood-borne transmission have been reported.

Clinical spectrum depend on the susceptibility and nutrition of the host as well as virulence and size of inoculums:

- ***Sub-clinical infection*** is more common than clinical disease, identified by a delayed hypersensitivity response to leishmania antigens (*Montenegro skin test*)
- ***Visceral leishmaniasis (kala-azar),*** is the commonest manifestation in children **(Fig. 10.19)** after an incubation period of 2–6 months, with (i) *Intermittent fever* without significant constitutional symptoms, (ii) *Gross splenomegaly* with hepatomegaly, (iii) Moderate to severe *anemia* and *weight loss*, and (iv) dry, rough skin with dark pigmentation (kala-azar) over forehead, face and bony prominences.

  Typical *double-rise fever* of kala-azar is uncommon in children. Long-standing cases may develop signs of *hypersplenism*, i.e. severe anemia, bleeding tendency and recurrent infections, as well as signs of *hepatocellular failure,* e.g. jaundice, edema and ascites. Untreated cases are usually fatal.
- ***Post kala-azar dermal leishmaniasis*** is rare in childhood, seen after many years of treatment and cure of visceral disease with development of multiple hypopigmented, erythematous or nodular lesions over face, back and extensor aspect of extremities, which persist for many years before disappearance.

Fig. 10.19: **Kala-azar: Clinical (cachexia with splenomegaly).**

- ***Rare presentations,*** uncommon in India, include localized or diffuse cutaneous leishmaniasis (O*riental sore*) or mucosal leishmaniasis.

Kala-azar in HIV-infected population is an opportunistic infection, presenting as reactivation of old infection with prominent GIT involvement, without significant splenohepatomegaly.

Diagnosis depends on:

- *Clinical tetrad* of gross splenomegaly, anemia, failure to thrive and skin pigmentation, with/without fever, in a case from endemic region.
- Rapid diagnostic kits based on the antibody immunoassay with >90% sensitivity and specificity
- *Demonstration of LD bodies*, in splenic aspirate (>95%) or bone marrow aspirate (60–70%) **(Fig. 10.20)**.
- *Parasitic culture* from above samples on *Novy-McNeal-Nicolle* (NNN) media, are less sensitive but allow detection of promastigote form and species identification for epidemiological studies.
- *Serological tests*, e.g. ELISA test, using K39 antigen, is ~100% sensitive and specific. Others, e.g. indirect fluorescent antibody test are sensitive but do not differentiate between active and past infection.
- *Other laboratory abnormalities* include moderate anemia, leukopenia, thrombocytopenia and hypergammaglobulinemia (> 5 gm/dl).

Aldehyde test (Napier test) is a screening test, based on development of hypergammaglobulinemia in kala-azar. Add 1–2 drops of formalin in 1 ml of patient's serum. Milky-white opacification within 30 minutes indicates positive result. Test is positive after 2–3 months of the onset of illness and turns negative by 6 months of cure.

Leishmanin test-an intradermal test to assess cutaneous reaction to a promastigote suspension (leishmanin), is of no use for diagnosis of active kala-azar, but helps to distinguish immune (>5 mm induration) from non-immune subjects for epidemiological studies.

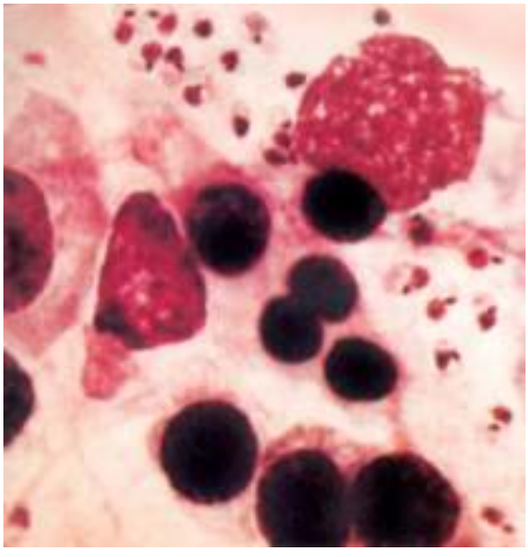

Fig. 10.20: Kala-azar: LD bodies (amastigote form of *L. donovani*).

Management of kala-azar aims to achieve clinical and parasitic cure, as well as to prevent relapses, by specific therapy and supportive measures, e.g. correction of anemia, undernutrition and intercurrent infections.

According to *operational guidelines for elimination of kala-azar in India 2015*, based on WHO recommendation, current treatment guidelines are as follows:

- Single-dose *Liposomal Amphotericin* (IV 10 mg/kg, infused over 2 hours) is the treatment of choice for all ages, including children.
- PO *Miltefosine* (2.5 mg/kg/d OD) for 28 days is an equally effective option with oral convenience, but should not be used in children <2 years, pregnant and lactating women and cases with Co-HIV infection.
- Amphotericin B deoxycholate (IV 1 mg/kg/dose over 8 hrs x 15 doses) may be used in refractory cases.
- Combination of Miltefosine (PO 2.5 mg/kg/d OD) *with* Paromomycin (IM 11 mg/kg/dose OD) for 10 days may be used, if IV liposomal amphotericin infusion is not possible.

Other drugs, e.g. sodium stibogluconate, pentamidine, etc. are no longer recommended due to treatment failures and toxicity. Oral therapy with ketoconazole or allopurinol is effective in cutaneous leishmaniasis but has no role in kala-azar.

Splenectomy is indicated only in cases with massive splenomegaly on the verge of rupture or associated hypersplenism.

All treated cases should be reassessed with splenic/marrow aspirate after 3 months to exclude late relapse, which should be treated as a fresh case.

Prevention of kala-azar depends on: (a) *controlling the source*, i.e. identification and adequate therapy of infected cases, (b) *controlling the vector* by residual insecticide sprays and sanitation measures, and (c) *personal prophylaxis* against mosquito bite by repellents and nets.

National Kala-azar Elimination Programme (2010) aims to reduce the annual incidence to < 1/10000 population at block PHC level in endemic districts and is being implemented under NVBDCP involving: (a) early diagnosis and complete case management, (b) integrated vector management and vector surveillance, (c) supervision, monitoring, surveillance and evaluation, and (d) IEC activities, with inter-sectoral convergence.

10.35 FILARIASIS

About 2/3rd of filaria cases in world are from three Asian countries, i.e. China, India and Indonesia. It is endemic

all over India, except in some northern and north-eastern states. National Health Policy (2017) aims to eliminate filaria, defined as achieving microfilaria rate of <1:10000 population in endemic regions.

Epidemiology: In India, 98% cases of filariasis are caused by *W. bancrofti*, and rest by a closely related *Brugia malayi* infection, limited to certain districts of Kerala.

Reservoir of infection is an infected man, harbouring adult worms of ~4–5 cm size in lymphatic system that live for many years. Female worm produces ~ 50,000 *microfilaria* (Mf) per day, which enter the circulation via lymphatics, usually at midnight (*nocturnal periodicity*).

Mode of transmission is a vector (Mosquito)-C*ulex fatigans* for bancroftian filariasis and *Mansonia annulifera* for brugian infection. After an infected feed, Mf exsheath in mosquito gut to develop as infective larva (10–14 days), which migrate to proboscis and injected into new human host during next bite.

After the infected bite in humans, infective larva are deposited near puncture-site and enter lymphatics, where they reside and develop as adult worm to produce Mf.

Clinical manifestations develop only in a small percentage of infected population, less common in children than adults and present as: (a) lymphatic filariasis, or (b) occult filariasis.

- ***Lymphatic filariasis*** may present as:
  - *Asymptomatic microfilaremia,* detected on night-smear examinations in endemic zones,
  - *Acute filariasis* in initial months of infection, with recurrent episodes of fever, lymphangitis, lymphadenitis, lymphedema and epididymo-orchitis, and
  - *Chronic lymphatic obstruction* due to fibrosis and block of lymphatic channels after many years, e.g. elephantiasis, hydrocele and chyluria (very rare in childhood).
- ***Occult filariasis,*** without signs of lymphatic disease, is more common in children and presents with tropical pulmonary eosinophilia or other immunological disturbances, e.g. arthritis, proteinuria, etc.

Diagnosis usually depends on:

- *Clinical features* of acute/obstructive disease in endemic area, supported by,
- *Night-smear:* Demonstration of Mf in thick peripheral smear **(Fig. 10.21)**, collected around mid-night *or* after one hour of 100 mg PO diethylcarbamazine administration (*Provocation test*);
- *Serodiagnosis* i.e demonstration of filarial antigens/antibodies, and
- *Biopsy/radiology* of affected part showing calcified, dead or living worm/s.

Fig. 10.21: Microfilaria: Peripheral smear.

TABLE 10.58: Diagnostic criteria for TPE

- Typical clinical episodes in endemic region
- Hypersensitivity indicators:
  - Absolute eosinophil count >3000 cells/mm^3
  - Elevated IgE levels (>1000 IU/ml)
  - Presence of anti-Mf antibodies
- Therapeutic response to DEC therapy

Treatment: Role of anti-filarial drugs in acute filariasis or chronic obstructive disease is controversial, as these drugs have no effect of infective larvae or ? adult worms. However, all Mf positive cases need specific therapy to reduce parasite load, as follows:

- PO *diethylcarbamazine* or DEC (6 mg/kg/d q8hr) for 14–21 days. Some workers recommend lower dose on first 2–3 days to avoid hypersensitivity reactions due to rapid death of Mf.
- PO *Ivermectin* (20–200 mg/kg) with/without PO albendazole (400 mg), as a single dose is equally effective to clear microfilaremia.

Tropical pulmonary eosinophilia is a common hypersensitivity manifestation against Mf or ? adult worms in school children of endemic regions.

Clinically these cases present with recurrent and paroxysmal asthma-like episodes of dry cough, wheeze and dyspnea; with/without mild fever, anorexia, hepatosplenomegaly and lymphadenopathy. Recurrent episodes may lead to interstitial fibrosis and chronic respiratory insufficiency.

Diagnosis rests on *a diagnostic criteria* **(Table 10.58)** among residents of an endemic region. Night smears for Mf may/may not be positive. X-ray chest may be normal except bronchovesicular prominence or reveals typical *miliary mottling*.

D/D of TPE includes other causes of paroxysmal cough with eosinophilia, e.g. asthma, Loeffler syndrome, drug allergy, fungal infections, sarcoidosis, lymphomas and rare hypereosinophilic syndromes.

Treatment involves oral DEC therapy for 21 days, which may be repeated in cases with partial response. Response is monitored clinically and by absolute eosinophil counts.

10.36 INTESTINAL PROTOZOAL INFECTIONS

Two most common intestinal protozoal infections in children include Amebiasis and Giardiasis, discussed here.

10.36.1 AMEBIASIS

Amebiasis, a common waterborne illness in India, is relatively less common in children than adults.

Epidemiology: Causative protozoan *Entamoeba histolytica* exists in two different forms—*cysts*, in contaminated water/food; and *trophozoites* in human intestines. Infection is acquired feco-orally on ingestion of parasitic cysts (not by trophozoites, which rapidly degenerate by gastric acid).

On ingestion, each cyst liberates eight trophozoites in small intestines, which are passed further to attach and penetrate colonic mucosa. Some trophozoites *encyst* again, to be excreted in stools.

Invasive trophozoites may multiply locally to produce *flask-shaped colonic ulcers* in cecum, transverse and sigmoid colon (*intestinal disease*) or enter portal circulation to invade liver (*extra-intestinal disease*).

Minimal local inflammatory response in colonic ulcers or at the site of extraintestinal disease is pathognomonic of amebic lesions.

Clinical spectrum: 90% of amebic infections are asymptomatic except intermittent passage of cysts in the stools (*carriers*). Symptomatic disease may be intestinal and extra-intestinal:

- ***Intestinal amebiasis*** manifests after 2–3 weeks of infection with gradual onset of: (a) diarrhea or dysentery with blood and mucus, (b) colicky abdominal pain or sense of fullness, (c) vague tenderness over iliac region, and (d) characteristic absence of constitutional features, e.g. high fever, toxemia, etc.

  Rare cases develop chronic colitis with recurrent bouts of dysentery and abdominal cramps, often confused with inflammatory bowel disease.
- ***Extraintestinal amebiasis*** is seen in <1% of infected cases, usually as hepatic abscess. Rarely, these abscesses may rupture in peritoneum, plural space or through the skin.

Amebic liver abscess usually involves the right lobe and may be single or multiple, filled with typical *anchovy-sauce* colored sterile pus. These cases present with—(a) fever with chills/rigors, (b) right hypogastric pain, and (c) tender hepatomegaly on deep palpation. History of intestinal disease and stool examination is negative in >50% cases.

TABLE 10.59: Common anti-amebic agents

Luminal amebicides		
Diloxanide fuorate	PO	20 mg/kg/d q8hr × 7 days
Di-iodoquinol	PO	30 mg/kg/d q8hr × 10 days
Paromomycin	PO	25–35 mg/kg/d q8hr × 7 days
Tissue amebicides		
Metronidazole*	PO	30–50 mg/kg/d q8hr × 10 days
Tinidazole	PO	50 mg/kg/d q24hr × 3 days
Secnidazole	PO	30 mg/kg single dose
Nitazoxanide	PO	100–500 mg BD × 3 days**

*or 20 mg/kg/d IV
**100 mg (1–3 yr), 200 mg (3–12 yr), 500 mg (>12 yr)

Diagnosis of *intestinal amebiasis* is confirmed by stool examination for cysts/trophozoites **(Fig. 14.2)**, while extraintestinal disease may be diagnosed by—(a) USG, (b) aspiration of suspected lesion to reveal *anchovy-sauce* pus with paucity of granulocytes, (c) indirect hemagglutination test (>1:128) with ~ 95% sensitivity.

Management: All children with *E. histolytica* in stools, even if asymptomatic, need to be treated. Metronidazole is the drug of choice for intestinal as well as extraintestinal disease, while luminal amebicides are preferred in asymptomatic case to eradicate carrier stage.

- *In symptomatic intestinal amebiasis*, a course of tissue amebicide, e.g. Metronidazole, Tinidazole or Nitazoxanide should be followed by a course of luminal amebicide, e.g. Diloxanide, paromomycin or Di-iodoquinol to ensure complete parasitic clearance **(Table 10.59)**.
- *In extra-intestinal amebiasis*, IV Metronidazole (20 mg/kg/day q12hr) is used for first few days, followed by oral therapy. Dehydroemetine or chloroquine are very rarely used in children. Amebic abscess needs to be drained only if-(a) poor therapeutic response after one week, (b) massive abscess with impending rupture.

Prevention depends on proper sanitation measures and boiling of drinking water. *Chlorination in usual doses is ineffective to destroy the parasite*. Stool examination of all cases and carriers should be repeated after 2 weeks of therapy to ensure parasitic clearance.

10.36.2 GIARDIASIS

Giardiasis is a common cause of chronic diarrhea or malabsorption in children, especially those with *poor sanitation, malnutrition, immunodeficiency states and institutionalization*, e.g. daycare centers or orphanages.

Epidemiology: *Giardia lamblia* exists in two stages—*cysts* in the environment and *trophozoites* in intestinal lumen. Infection is acquired feco-orally, after ingestion of contaminated water.

After ingestion, each cyst liberates 2–4 trophozoites, which colonize the *duodenum and proximal jejunum* (site of infestation) by attaching themselves to brush borders with their powerful sucking discs. Later, some detached trophozoites pass-down and encyst again, to appear in stools for further transmission.

Malabsorption in Giardia-infested children is attributed to—(a) mechanical damage to microvilli by trophozoite discs, causing disaccharidase deficiency, (b) pancreatic injury with reduced tryptic activity and (c) bacterial overgrowth in duodenum, causing bile-salt deconjugation.

Clinical manifestations: After incubation period of 1–2 weeks, giardiasis may manifest as:

- Asymptomatic excretion of cysts (carriers),
- Acute, explosive, watery, foul-smelling diarrhea, lasting for 3–4 days,
- Chronic malabsorption with intermittent diarrhea, steatorrhea, flatulence and failure to thrive.

Diagnosis requires demonstration of cysts or trophozoites in stools or *duodenal aspirate/biopsy*, later being the best specimen to detect asymptomatic infestation. At least 3 fresh stool samples should be examined for giardia, collected on alternate day after discontinuation of anti-parasite drugs **(Fig. 14.2)**.

Serodiagnosis of giardia antigen in stools, using monoclonal antibodies is possible, but rarely used.

Management: All cases including asymptomatic carriers need treatment with:

- PO Metronidazole (15 mg/kg/day q8hr) for 5 days, *or*
- PO Tinidazole (50 mg/kg single dose above 3 years), *or*
- PO Nitazoxanide (100 mg 1–3 yr, 200 mg 3–12 yr, 500 mg >12 yr per dose, BD × 3 days), or
- PO Albendazole (400 mg OD × 5 days, above 6 years)

Repeat stool exam is necessary to ensure eradication of infection. Persistence of infection despite repeated therapy indicates possible immunodeficiency state.

Prevention depends on improved sanitation and safe water supply. Micropore filtration (<5 mm) or boiling of drinking water is effective to eliminate/kill the cysts, but *chlorination in usual doses or ultraviolet radiation is ineffective.*

10.37 INTESTINAL WORM INFESTATIONS

Intestinal worm infestations are estimated to be present in ~20% of under-five children in India and WHO classifies India as a moderated-risk country for worm infestations. Some important worm infestations in children are as follows.

Ascariasis: Ascariasis (*round worm*) is the ubiquitous worm infestation of mainly pre-school and early-schoolchildren, specially in low-hygiene population.

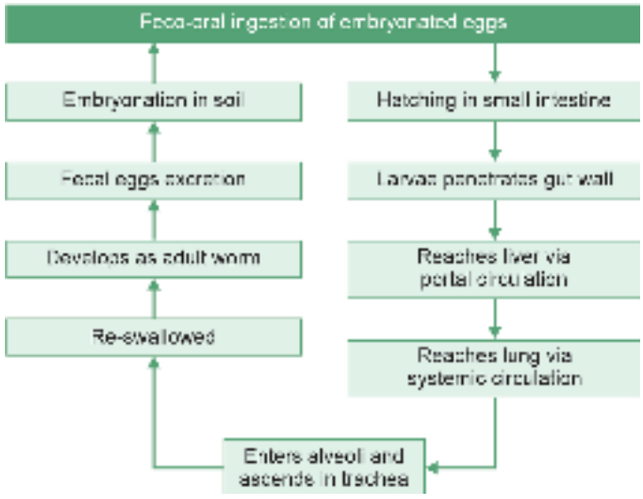

Fig. 10.22: **Life cycle of *Ascaris lumbricoidus*.**

Life-cycle: Heterosexual adult worm (*A. lumbricoidus*) lives in small intestine, with a lifespan of 1–2 years. Female worms are longer (20–30 cm) than males (12–20 cm) and lay up to 2 lac eggs/day, which are excreted in feces. These eggs embryonate in soil and turn infective after 2–3 weeks.

Infective (larva-containing) eggs are *feco-orally* transmitted to another host via soil-contaminated fingers or uncooked food items. Promiscuous defecation and use of human feces as manure are two important risk factors in transmission.

On ingestion, eggs hatch in small intestine and larva penetrate the gut wall to reach the liver and then the lungs via blood stream. In lungs, they mould twice before breaking alveolar walls to enter bronchioles, ascend to trachea and re-swallowed. On reaching the intestine second-time, these larvae develop into mature worms, lay eggs and continue the cycle **(Fig. 10.22)**.

Clinically, ascariasis is asymptomatic or present with:

- *Vague features,* e.g. abdominal discomfort, malabsorption and undernutrition in heavy infestation.
- *Mechanical obstruction,* e.g. airway obstruction during larval migration, intestinal obstruction due to mass of adult worms, or rarely, biliary obstruction by migrating worm with obstructive jaundice.
- *Immune-mediated* pulmonary manifestations, e.g. Loffler-like syndrome.
- Passage of adult worms in stools/vomitus.

Diagnosis depends on: (a) history of passing worms in stools/vomitus, *or* (b) stool microscopy (*Kato's thick smear*) to demonstrate presence of fertilized/unfertilized eggs **(Fig. 14.2)**. Presence of fertilized eggs in stool indicates bi-sexual infestation.

Treatment of choice is single oral dose of Albendazole 400 mg (200 mg < 2 yrs). Alternatives include other oral wormicidal drugs, e.g. Mebendazole (100 mg BD x 3 days)

or Ivermectin (150–200 µg/kg once). Nitazoxanide, a broad-spectrum drug may also be used orally as 100 mg BD x 3 days (400 mg BD in 4–12 years age group and 500 mg BD in adolescents).

In cases with intestinal or biliary obstruction, *Piperazine citrate* is preferred due to its neuroparalytic reaction on worms, which facilitates their expulsion. Surgical intervention may be needed in cases with severe obstruction.

Prevention: Community load of round worm may be reduced by: (a) mass deworming of pre-school children every 3–6 months, (b) hygienic sanitary/excreta-disposal practices, and (c) reduced use of human feces as manure.

Toxocariasis *(visceral* or *ocular larva migrans)* is an accidental human infestation by primarily zoonotic ascarids, i.e. *T. canis* (dogs) or *T. catis* (cats).

Life-cycle involves excretion of eggs in animal excreta > accidental feco-oral infection of children via contaminated fingers or food > hatching and larval release > gut penetration > migration to different tissues, e.g. lungs, liver, eyes, brain, etc. Toxocara larva do not develop beyond this stage in human host (*no adult worms*).

Clinically, these cases may present with: (a) *immunological reactions*, e.g. fever, hepatomegaly, urticaria, Loffler syndrome, or (b) *mechanical damage* due to migrating larvae, e.g. sudden decrease in visual acuity or blindness (*ocular larva migrans*).

Diagnosis rests on visualization of larvae in the tissues or an antibody-ELISA test (rarely available). History of frequent dog/cat exposure and eosinophilia is common.

Treatment is non-specific, including steroids for allergic manifestations, e.g. urticaria or Loffler syndrome. Antihelminthic therapy (PO Albendazole 400 mg BD × 5 days) is indicated only in symptomatic cases, along with steroids to reduce inflammatory response to antigens released from dying parasites. Longer therapy for 3–4 weeks is needed in ocular or neurological disease.

Enterobiasis: Enterobiasis (*Threadworm or Pinworm*) is the commonest worm infestation in pre-school children, which is essentially harmless except inconvenient perianal itching.

Life-cycle: Causative adult worm *E. vermicularis* is ~0.5–1 cm in size and lives in caecal region of infested human host. Gravid female migrates externally through the anus during night, to lay eggs over perianal area. These eggs mature here as infecting larvae in 6 hours and remain viable for next 20 hours.

While a new host is infected feco-orally, same host may also be re-infected by *auto-inoculation* of eggs, carried under fingernails after perianal scratching. On ingestion, these eggs hatch in stomach, larvae migrate to caecal region and mature as adult worms to continue the cycle **(Fig. 10.23)**.

Fig. 10.23: Life cycle of *E. vermicularis*.

Clinically, *nocturnal perianal pruritis* is the commonest manifestation of enterobiasis, leading to disturbed sleep. Very rarely, perianal granuloma containing live/dead worms or eggs have been reported.

Diagnosis: As eggs are generally not passed in stools, definitive diagnosis depends on demonstration of eggs **(Fig. 14.2)** in perianal region *or* adult worms in stools or at perineal region.

Best method to demonstrate enterobius eggs is to stick an adhesive cellophane tape against perianal region in early morning and examine under microscope.

Treatment of choice is single oral dose of Albendazole 400 mg (200 mg < 2 years), though alternatives include other wormicidals, e.g. Mebendazole (100 mg once) or Pyrantel Pamoate (11 mg/kg base TDS x 1 day). It is to be noted that:

- Treatment should be repeated after 2 weeks in all cases, to eradicate residual infestation, and
- All family members should be treated simultaneously, to prevent cross-infection.

Soothing creams, e.g. crotamitone, may be applied to relieve perianal itching and prevent auto-inoculation.

Prevention: Personal cleanliness with regular trimming of nails and periodic de-worming of susceptible population are important measures to prevent threadworm infestations.

Trichuriasis (Whipworm) is a common infestation in children, though rarely diagnosed due to lack of symptoms.

Life cycle: Adult worm *T. trichuria* (~ 3–4 cm) lives in cecum and ascending colon, firmly anchored to mucosa to suck ~ 0.005 ml blood/day. Infection is transmitted feco-orally, on ingestion of embryonated eggs in contaminated hands, food or water.

Clinical manifestations are rare and include: (a) vague abdominal discomfort, e.g. colic or distension, or (b) mild anemia, bloody diarrhea or rarely rectal prolapse in heavily parasitized host.

Diagnosis depends on stool examination for typical eggs **(Fig. 14.2)**.

Treatment of choice is PO Albendazole 400 mg x 3 days (200 mg < 2 years), though alternatives include PO Mebendazole 100 mg BD or Ivermectin 200 µg/kg/d, both for 3 days.

Ankylostomiasis: Ankylostomiasis (*Hookworm* infestation) is an important cause of iron deficiency anemia in Indian children, usually caused by *Ancylostoma duodenale,* and occasionally by *Necator amaricanus*.

Life cycle: Hetrosexual adult worm (5–13 mm) lives in small intestine, firmly attached to the gut mucosa with their typical hooks or teeth. Female worms produce up to 30,000 eggs/day, which are excreted in stools to develop as infective larvae in warm and damp soil.

Infection is usually acquired via *cutaneous penetration* over feet, especially in bare-foot walkers (rarely feco-oral). After skin-penetration, larvae enter the venous circulation to reach lungs, where it comes out of the vascular bed to enter in alveoli, ascend into airways and get swallowed. On reaching the small intestine, it develops into adult worms, attaches itself to intestinal walls and starts oviposition **(Fig. 10.24)**.

Bare-foot walking on infested soil, poor sanitary conditions and use of human feces as manure, are the main risk factors for hookworm infestation, which is common in rural and slum population.

Clinically, *anemia* due to intestinal blood loss by hooked attachment of adult worms is the most important manifestation of ankylostomiasis and its severity depends on worm-load. *Each adult worm is responsible for ~ 0.2–0.3 ml of blood loss per day*.

Other manifestations include: (a) non-specific GIT problems, e.g. abdominal pain, anorexia, diarrhea, and melena; (b) localized itching (*ground-itch*) at the site of skin entry*, and rarely, (c) transient stridor or pharyngitis, during airway migration of larvae.

*Typical *cutaneous larva migrans* is seen only with some zoonotic worms, e.g. A. braziliense.

Diagnosis should be suspected in cases with unexplained anemia and occult blood in stools, confirmed on stool examination for eggs **(Fig. 14.2)**.

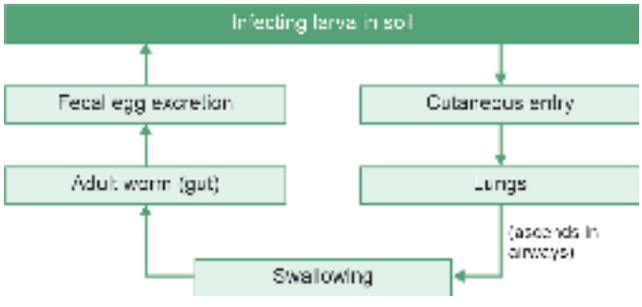

Fig. 10.24: **Life cycle of Hookworm *(A. duodenale)***.

Treatment of choice includes single oral dose of *Albendazole* 400 mg (200 mg < 2 years), though alternatives include other oral wormicidal agents, e.g. Mebendazole 100 mg BD x 3 days or Pyrantal pamoate 11mg/kg/day OD for 3 days. Repeated doses may be required for complete eradication.

In addition, these patients also need correction of anemia by oral iron therapy or rarely blood transfusions.

Prevention depends on community measures, e.g. (a) periodic deworming, (b) avoidance of bare-foot walking, (c) improvement of sanitation and excreta disposal, and (d) reduced use of fecal manure.

Strongyloidosis *(S. stercolaris)* is an uncommon infestation, acquired via skin penetration by infective larvae in feces-contaminated soil.

Life-cycle is similar to hookworm, except that eggs often hatch *in vivo* during intestinal passage and infective larvae re-enters the circulation by penetrating intestine walls or perianal skin (*auto-inoculation)*.

Clinically, it is asymptomatic or present with: (a) perianal itching due to auto-inoculation (*larva currens)*, (b) Loeffler's-like syndrome with eosionophilia due to larval migration through lungs, (c) malabsorption syndrome in heavy infestations, and (d) rarely, *disseminated strongyloidosis*—a septicemia-like illness in severely malnourished or immunocompromised children.

Diagnosis depends on examination of stools or duodenal aspirate for characteristic larvae.

Treatment: PO Ivermectin (200 µg/kg/d) for 1–2 days is the drug of choice. PO Thiabendazole 50 mg/kg/d q12hr is an alternative, specially in disseminated disease.

Cestodal (Tapeworm) infestations: Human cestodal (tapeworm) infestations present in two forms—(a) *intestinal infestation* by adult worms, and (b) *tissue infestations* by invasive stages, e.g. hydatid cyst and neurocysticercosis.

a. ***Intestinal tapeworm infestations*** are less common in children than in adults, caused by *Taenia solium* (Pork tapeworm), *T. saginata* (Beef tapeworm), *Diphyllobothrium latum* (Fish tapeworm) and *Hymenolepis nana* (Dwarf tapeworm).

Life-cycle: These infestations are acquired by ingestion of—(a) parasitic eggs, present in contaminated soil/water or over the body of intermediate hosts; *or* (b) uncooked beef, pork or fish, containing invasive stages of parasite.

Adult tapeworms are present only in human intestines and have long, segmented (*proglottids*) bodies of variable length (fish tapeworm is longest, 10–20 meters). On maturation, caudal gravid segments detach intermittently to pass in stools and release eggs in the soil.

Although entire life-cycle may be completed in humans alone (except *D. latum**), animals, e.g. dogs, pigs, cattle, etc. are frequently infected by ingestion of egg-contaminated soil *or* invasive-stage-contaminated flesh of infected animals, to contribute in propagation of disease (*Co-hosts*).

**D. latum* requires hatching of eggs in fresh water and subsequent passage of embryo through two intermediate hosts, i.e. *copepods*—small crustaceans, which swallow the eggs/larvae and *fishes* that eat these crustaceans, before re-infecting humans on ingestion of uncooked fish.

Clinically, intestinal tapeworm infestation is asymptomatic or presents with vague abdominal complaints, except *D. latum infestation, which may cause megaloblastic anemia* by inhibiting vitamin B12 absorption and utilizing it for own metabolism.

Diagnosis depends on presence of proglottids (on naked eye) or eggs (on microscopy), in stools *or* rectal swabs.

Treatment of choice for all intestinal tapeworms is single oral dose of Praziquantel (25 mg/kg) or Niclosamide (50 mg/kg). PO Nitazoxanide 100 mg BD x 3 d (400 mg BD in 4–12 years age group and 500 mg BD in adolescent and adults) may also be used. Simultaneous treatment with polyethylene glycol can increase fecal yield of scolices.

Prevention involves adequate sanitation, proper excreta disposal and avoidance of eating uncooked meat/fish.

b. ***Hydatid cyst*** is caused by intermediate (invasive) form of *Echinococcus granulosus*-a zoonotic tapeworm in dogs or other canines.

Pathogenesis: Humans are accidentally infected by ingestion of the intermediate forms of parasite, present in contaminated water/food or over fecal-contaminated body of infected dogs. Ingested intermediate forms penetrate the gut-wall, carried via lymphatics/blood to liver, lung, bones, etc., and develop into gradually enlarging cysts.

Structurally, these cysts are surrounded by a tough fibrous capsule of host tissue, lined by inner layers of parasitic origin and contain thousands of parasites (*protoscolices*) along with cystic fluid.

Clinically, lung cysts are more common in children, while liver cysts are commoner in adults. Hydatid cysts may be asymptomatic or present with mass effect, i.e. (a) hepatomegaly with palpable mass and pain in liver cysts, (b) cough, hemoptysis and chest pain in lung cysts, and (c) pathological fractures in bone cysts.

Complications include: (a) cyst rupture (spontaneous or during surgery) which may lead to sudden anaphylaxis and/or formation of secondary cysts, and (b) pressure on other structures, e.g. biliary tree with obstructive jaundice.

Diagnosis depends on: (a) *ultrasonography*, i.e. cystic lesion with internal membranes and floating echogenic cyst material (*Hydatid sand*), and (b) *Casoni's skin test*, to detect hypersensitivity against crude or partially purified antigen. It may be false-negative in 50% cases and false-positive in other tissue helminthes, e.g. neurocysticercosis or schistosomiasis.

Treatment depends on the size and site of cyst and includes:

- *Conventional surgical removal* of cyst as a whole (except outer fibrous wall) for large and complicated cysts,
- *PAIR technique*, i.e. USG or CT guided ***p***ercutaneous ***a***spiration > ***i***nstillation of hypertonic saline or other scolicidal agent > ***r***e-aspiration after 15 minutes. PAIR is contraindicated in pregnancy or bile containing cysts.
- *Medical therapy* for multiple, small, deep-seated cysts, with albendazole (PO 7.5 mg/kg BD) for 1–6 months. Medical therapy is also indicated when surgery is contraindicated or one week before and one month after PAIR.

c. ***Neurocysticercosis*** (NCC) is the commonest parasitic infection of CNS, caused by the invasive intermediate stage of *T. solium* (pork tapeworm), with formation of asymptomatic or symptomatic cysts in the brain (*see* Ch 18.12.9 for details).

Trematodal (Fluke) infestations are uncommon in Indian children and characterized by their typical life-cycle involving two hosts-man for sexual phase and snails for asexual phase.

According to preferential tissue-habitat, trematodal infestations are also termed *Blood flukes,* (*Schistosoma hematobium*) *Liver flukes* (*Fasciola hepatica, Clonorchis sinensis*) and *Lung flukes* (*Paragonimus westermani*).

Schistosomiasis is the commonest trematodal infestation, acquired via *cutaneous penetration* by the infective larvae, i.e. *cercariae,* present in contaminated water bodies and on aquatic plants. Post-entry, cercariae migrates via subcutaneous tissue, lungs and liver; and develops as adult worms (sexual stage) that reside in the venous plexus surrounding ureters and urinary bladder.

Oviposition occurs intravascularly and eggs are intermittently excreted in urine, after rupture of invaded capillaries. Further development from egg to infective larvae (asexual stage) occurs only in *fresh-water snails* (intermediate host), to continue the cycle.

Clinically, these cases present with—(a) local pruritic rash at the portal of entry (*Swimmer's itch*), (b) acute febrile illness with eosinophilia after 4–8 weeks of infection (*Katayama fever*), or (c) chronic granulomatous injury at the site of parasitic deposition, e.g. periureteic/perivesicular venous plexus, leading to hematuria.

Diagnosis depends on urine examination for schistosome eggs.

Treatment of choice is PO Praziquantel 20 mg/kg, total two doses at 12-hour interval.

10.38 NOSOCOMIAL INFECTIONS

Nosocomial infections, defined as *infections acquired during or as a result of hospitalization* are major cause of morbidity and mortality in hospitalized children. Generally, *All new infections, manifesting after 48 hours of hospitalization are considered as nosocomial*, unless proved otherwise.

Incidence of nosocomial infections in general hospital wards is estimated to be ~ 3–5%, but may be as high as >40–50% in post-operative wards, intensive care units, high-risk patients, and after prolonged hospitalization.

Epidemiology of nosocomial infections varies from hospital to hospital and even within the hospital from ward to wards.

Sources: Hospital flora is full of pathogenic and seemingly innocuous organisms that keeps on changing time to time. Nosocomial infections may originate from:

- *Inanimate objects*, e.g. (a) hospital floorings, walls, furnitures, fixtures, linens, etc. (b) water supply and sanitation closets, (c) resuscitation or other equipment, e.g. catheters, nebulizers, ventilators, etc., or (d) shared use sources, e.g. suction apparatus, oxygen bottles/tubings, dressings, antiseptic solutions, etc. *or*
- *Animate objects*, e.g. (a) asymptomatic/symptomatic hospital persons, visitors and other patients and (b) patient's own flora, i.e. *auto-inoculation* during aspiration and IV lines.

Mode of infection: Nosocomial infections may be acquired via multiple routes, e.g.

- *Direct contact* with unsterilized equipments or infected hands of hospital personnel,
- *Inhalation* of suspended organisms, i.e. droplet infections,
- *Ingestion* of contaminated hospital-food and medicines,
- *Vector-borne* spread from flies and mosquitoes,
- *Auto-inoculation* from own flora, e.g. aspiration or IV lines.

High-risk factors: Although all patients in a hospital ward are exposed to nearly similar risk for colonization with hospital pathogens, some are more susceptible to develop nosocomial infections than others **(Table 10.60)**. Apart from these host-related factors, infection control practices, antibiotic policy and waste-management policies of the hospital are important determinants of nosocomial infections.

Clinico-microbial profile: Nosocomial infections may be caused by any normal or opportunistic organisms (OIs) present in the hospital environment, depending on the source. Common nosocomial infections in children are as follows:

TABLE 10.60: High-risk host factors for Nosocomial infections

- Newborns and young infants
- Immunocompromized states
- Critically sick, debilitated or unconscious child
- Surgical, oncological or burn cases
- Invasive devices, e.g. vascular catheters
- Prolonged antibiotic therapy
- Prolonged hospitalization

- ***Respiratory tract infections*** account for 25–30% of nosocomial infections, more common in cases with airway interventions (oxygen, nebulizers, ventilators, intubation/tracheostomy) *or* high-riskof aspiration (debilitated or unconscious children). Most of them are caused by *Staph. aureus* and *Pseudomonas.*
- ***Urinary tract infections*** are common in general wards (40–45%), specially prevalent in cases with indwelling urinary catheters, genitourinary surgery and urinary retention/incontinence, these infections are usually caused by *gram negative bacilli,* e.g. Klebsiella; coagulase negative staphylococci (CONS); and enterococci, etc.
- ***Surgical wounds and burn infections*** (5–7%) are common in cases with poor wound drainage or infected dressings. These infections are usually caused by *Staph. aureus, Pseudomonas and CONS*; though enterococcal and anaerobic infections are common in feces-contaminated wounds.
- ***Vascular-catheter related infections*** (~3–5%) are more likely with central vascular lines, prolonged peripheral IV therapy and total parenteral nutrition. Risk of bacteremia/septicemia in these cases is directly related to duration of cannulation. Microbial agents in catheter-related infections are usually derived from normal skin flora, e.g. *CONS, anaerobes and Staph. aureus*, although candidemia is also common after prolonged cannulations.
- ***Gastrointestinal infections,*** e.g. enterocolitis (~8–10%) are common in patients with prolonged antibiotic therapy (*Candida, C. defficile*) or hospital-diet (*Salmonella*).
- ***Skin infections*** of nosocomial etiology are common at IV or monitor-probe sites. Most of them are *staphylococcal* in origin (*Staph. aureus* or CONS), though candidal infections may develop at macerated skin sites, e.g. back-sores.
- ***Immunocompromised hosts*** are specially susceptible for *candidal and anaerobic infections*, as well as serious bacterial infections due to *Staph. aureus* and Pseudomonas.
- ***Transfusion-related infections*** develop immediately after receipt of blood/products, e.g. sepsis, malaria; or after many months/years, e.g. HIV, HBV, etc.

Prevention of NIs is one of the most important aspects in management of intensive care. Each hospital should have—(a) written hospital *infection control policy*, (b) efficient *surveillance system* to identify changing microbial profile, antibiotic-sensitivity patterns and new nosocomial outbreaks, and (c) periodically review of *antibiotic policy*, consistent with changing hospital flora. Important components of hospital-infection control measures include:

- Maintenance of environmental hygiene
  - General cleanliness, e.g. regular vacuum cleaning or wet-floor mopping with antiseptics.
  - Adequate sunlight and wind-movements. Air-conditioner filters should be cleaned regularly.
  - Restricted use of curtains and decorative items.
  - Periodic fumigations, specially if an outbreak is suspected.
  - Proper bio-medial waste disposal.
- Prevention of cross-infection
  - Strict handwashing (discussed below).
  - Minimum handling of patients.
  - Isolation of highly septic/infectious cases.
  - *Barrier nursing* for immunocompromised host.
  - No overcrowding (restricted visitors).
  - Use of mask, gloves, etc., whenever indicated.
- Prevention of device-related infections
  - Use of disposable instruments/devices.
  - Proper sterilization of equipments.
  - Frequent change of invasive catheters.
  - Regular cleaning of suction and oxygen bottles.
- Rational use of antibiotics
- ***Regular surveillance*** for:
  - Hospital flora (cultures from various sites).
  - Microbial profile to decide antibiotic policy.
  - Early detection and control of NIs outbreaks.
- ***Health education*** of hospital staff
- ***Minimum hospitalization,*** as far as possible.

Handwashing is the most effective control measure against nosocomial infections. Important steps **(Fig. 10.25)** for proper handwash include:

a. Remove the watch and jewellery,
b. Wash with soap and running water, with special attention to inter-digital areas,
c. Minimum duration of wash – 3 minutes before the first handling and 30 seconds in-between the patients,
d. Dry under automatic hand drier or with disposable sterile napkins.

Use of antiseptic solutions, e.g. alcohol, cetrimide, chlorhexidine or iodine solutions, etc. for handwash is no way superior to simple soap and running water wash, though may be practiced in special circumstances.

Outbreak control measures in a suspected outbreak of NI include:

Fig. 10.25: Correct handwashing technique.

- Confirming the outbreak by review of records.
- Identification of index case and contacts.
- Barrier or *cohort nursing* for suspected cases.
- Search for the source of infection* and remedial measures.
- General measures, e.g. fumigation and post-fumigation swab-cultures from various sites.
- Continuous surveillance to further cases.

*Search for the source involves environmental cultures, cultures from probable inanimate sources, e.g. suction bottles; as well as nasopharyngeal cultures from health-care personal.

Biomedical Waste Disposal

Biomedical waste is defined as '*any waste, generated during the diagnosis, treatment, or immunization of human beings and animals as well as during related research activities*'.

Nearly 75–90% of this waste is comparable to any domestic waste, without any additional health-risk.

However, remaining 10–25%, containing biological tissues and secretions, drugs, sharp devices, etc.

TABLE 10.61: Essentials of bio-medical waste disposal

Color code	*Type of waste*	*Container*	*Method of disposal*
Yellow	Biological waste*	Plastic bag	Incineration *or* deep burial
Red	Reusable, non-sharp waste	P. bag/sterile container	Autoclaving, chemical, microwave
Blue	Sharp waste	Puncture-proof container	Shredding > disinfection > recycling
Black	Drugs and chemicals	Plastic bag	Land-burial

*Blood, tissues and laboratory samples

Is potentially harmful and needs to be disposed carefully. Important steps in biomedical waste disposal (as per GOI rules, 1998) include:

- ***Segregation*** of the waste at ward-level, in suitable *color-coded* containers **(Table 10.61)**.
- ***Transport*** to disposal sites by proper means, e.g. covered trucks without spillage.
- ***Proper method of disposal,*** e.g. incineration, dumping, burning, etc.

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CHAPTER

11

Genetic Disorders

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Since the discovery of the principles of inheritance (*Gregor Mendel*, 1865), genetic composition of a cell is considered as the blueprint of life. Genetic disorders are estimated to affect ~4–5% of all live births, though exact prevalence is considerably higher as many genetically defective conceptions die *in utero* or remain undetected throughout the life.

Modern genetics is a rapidly expanding science in the man's quest to understand the origin of human disease. Recent advances, including new methods in molecular diagnosis and gene manipulation have revolutionized the scope of prevention and treatment of genetic disorders.

11.1 BASIC CONSIDERATIONS

Human genome: Each human somatic cell contains two copies of the entire genetic program, i.e. g*enome*, *each* encoded in 3 million base pairs of DNA. However, less than 2% of human DNA is functionally active, rest being *junk or redundant DNA,* for which exact function are not yet known. Most, but not all, of the DNA is contained in the nucleus, rest being in mitochondria or scattered in cytoplasm.

DNA: DNA (deoxyribonucleic acid) is a double-stranded chemical structure, resembling a long and twisted rope ladder, i.e. *helix*. Each *side* of this ladder is made up of pentose sugar and phosphate molecules and each *step* comprises a pair of nitrogenous bases, termed base pairs (bp).

Human DNA contains four nitrogenous bases—two purines, i.e. Adenine (A) and Guanine (G); and two pyrimidines, i.e. Cytosine (C) and Thymine (T). Of these, *A* always pairs with *T*, and *C* with *G* **(Fig. 11.1)**. The order of this *bp* arrangement varies from the site to site on a DNA strand, denoted as *DNA sequence.* DNA sequence at a specific DNA locus determines its role in genetic functions.

Chromosome: Entire DNA material in the somatic human cell nucleus is packaged in 23 pairs of chromosomes (n = 46), including 22 pairs of somatic chromosomes

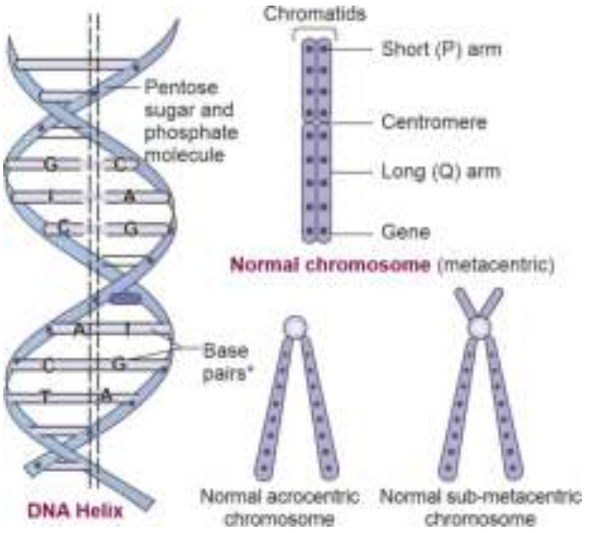

Fig. 11.1: Basic structure of DNA and chromosomes
*C: cytosine; T: Thymine; A: Adenine; G: Guanine

(*autosomes*) and a pair of sex chromosomes (XX in females and XY in males). A baby receives one chromosome of each autosomal pair from different parents, one sex chromosome from father (X or Y) and another sex chromosome (X) from mother. Unlike somatic cells with paired chromosomes, (i.e. *diploid cells*), germ cells, e.g. sperms or eggs contain only 23 unpaired chromosomes, (i.e. *haploid cells*).

Morphologically, somatic chromosomes are of variable size and numbered according to its size in decreasing order-the largest being chromosome 1 and the smallest being chromosome 21. Sex chromosomes are not numbered, identified by their size and morphology. X is a large submetacentric chromosome, while Y is a small acrocentric chromosome.

Each chromosome consists of two identical thin strands (sister *chromatids*), with a short arm (p), long arm (q) and joined together by a centromere **(Fig. 11.1)**. According to the location of centromere, chromosomes are also classified as *metacentric* (central centromere), *submetacentric* (centromere towards the short arm) and *acrocentric* (centromere at one end).

Gene: Gene is a functional unit of DNA, which codes for various proteins required for to govern various functions of the body. Each gene has a *unique* bp sequence, size, and location on a specific chromosome.

While over 1,00,000 genes are encoded in human DNA, all are not biologically active and some are active only in a particular cell, e.g. globin genes in RBCs. However, biologically inactive genes are not necessarily inert and some of them play important roles in modulation of the functions of biologically-active genes.

Genes with similar function, (e.g. globin chain synthesis) tend to cluster on a particular region of chromosome and may be switched-off and switched-on, at various stages of life. For example, γ-globin gene, which determines synthesis of fetal Hb *in utero* is turned-off at birth, when β-globin gene is activated to produce adult Hb.

Each gene regulates synthesis of specific proteins and contains two functionally different regions, i.e. *exons*—which code its biological activity, and *introns*—which are either functionally inert or act as regulator of exons.

As one chromosome in each pair is derived from different parents, every gene on one chromosome has a counterpart gene at the identical location (*homologous loci*) on other chromosome of the pair, together termed as ***alleles*.** Allelic genes are *analogous*, i.e. affect the same biological characteristics, but not necessarily *identical*. An individual is termed *homozygous*, if both alleles of a genetic pair carry identical biological information (normal or abnormal) and *heterozygous*, if they are non-identical.

Penetrance and expressivity: All genetic traits (*genotype*) do not necessarily manifest externally (*phenotype)* due to many factors including variable penetrance and expressivity of the Gene.

- *Penetrance* refers to the percentage of individuals with a specific genotype express in terms of corresponding phenotype, e.g. 80% penetrance means that 8 out of the 10 individuals carrying that particular gene manifest its effects.
- *Expressivity* refers to the degree that a particular genotype is expressed as phenotype in different persons, e.g. different severity of the disease despite same genetic defect.

Further, a gene may also not manifest due to presence of another dominant gene for same character (allele) on the other chromosome from different parental source, e.g. in autosomal or x-linked recessive inheritance, discussed later.

Transfer of genetic information for parental to daughter cells occurs during the cell division via transfer of DNA as chromosomes and constituent genes. Process of cell division may be divided into two types—*meiosis* and *mitosis*.

Meiosis is a two-step process that ultimately ends in formation of *haploid* germ cell. Subsequent fusion of two haploid germ cells from different parents restores normal diploid number in zygote, from which the new life begins.

Mitosis is characterized by replication of chromosomes before the cell division, so as to form two genetically identical, i.e. *diploid* daughter cells.

Mutation: All biological functions of a living cell are mediated by amino acids or proteins, e.g. enzymes. Genes are prime regulators of specific amino acid synthesis, essential for corresponding cell function.

Mutation (or variant), refers to a *heritable change in the DNA sequence of the gene,* which may or may not affect the structure and function of corresponding protein. Mutations may be of three types: (a) *point mutations* or substitutions replacing single nucleotide from another; (b) *deletions* involving loss of one or more nucleotides in the gene; and (c) *insertions*, i.e. addition of one or more nucleotide in the gene. Each mutation may be benign, pathogenic or of unknown significance, based on the effect on phenotype. While germline mutations usually cause monogenic disorders, somatic cell mutations may cause cancers.

Sequence variations without any obvious disease-causing effect are termed as *Polymorphism*.

Mutations may occur naturally as *chance* errors in DNA replication during chromosomal division or may be due to external teratogens, e.g. ionizing radiation or chemical exposures.

11.2 MODES OF GENETIC INHERITANCE

According to the mode of transmission and inheritance, Genetic disorders may be classified into various types, as follows **(Table 11.1)**:

1. Chromosomal Disorders

Chromosomal abnormalities are either numerical or structural and may be inherited from parents or arise *de novo* during gametogenesis by following mechanisms:

TABLE 11.1: Classification of genetic disorders

- **Chromosomal disorders**
  - Numerical abnormalities
  - Structural abnormalities
- **Single gene (Mendelian) disorders**
  - Autosomal recessive or dominant
  - X-linked recessive or dominant
  - Y-linked inheritance (non-pathogenic)
- **Multifactorial or polygenic disorders**
- **Mitochondrial disorders**
- **Alternate modes of inheritance**
  - Genomic imprinting
  - Uniparental disomy
  - Mosaicism
- **Somatic cell disorders**

- *Meiotic nondisjunction*, i.e. failure of a pair of chromosome to separate during meiosis. Consequently, one germ cell contains both members of chromosome pair (trisomy), while other lacks both (monosomy). *Advanced maternal age* is a major risk factor for meiotic nondisjunction.
- *Anaphase lag*, i.e. failure of one chromosome of a pair to move towards the opposite pole of dividing cell during anaphase of cell division *despite separation*, is another important source of numerical chromosomal abnormalities.
- *Mitotic nondisjunction (mosaicism)*, i.e. failure of the separation of a pair of chromosome in diploid zygote, during initial cell divisions after fertilization. Consequently some of the individual cells are trisomic, while rest are monosomic. Mosaic defects tend to be less severe or sub-clinical.

Numerical chromosomal abnormalities include the number of chromosomes being other than the haploid number (23) of germ cells or diploid number (46) of somatic cells. *Aneuploidy*, the commonest numerical abnormality, refers to number of chromosomes being other than in *multiples* of haploidy, due to more chromosome/s (47XY/XX or Down syndrome) or less chromosome/s (44XO, Turner syndrome). Other numerical abnormalities include *Euploidy* and *Polyploidy* **(Table 11.2)**.

Structural chromosomal abnormalities include (a) ***Deletion,*** i.e. loss of a DNA segment, (b) ***Translocation,*** i.e. separation of a DNA segment from one chromosome and re-attachment on another chromosome, and (c) ***Inversion,*** i.e. separation of a DNA segment from one chromosome and its re-attachment on the same chromosome but in reverse order. Mutual exchange of DNA segments between two chromosomes is termed as *Reciprocal translocation.* However, *inversion* or *reciprocal translocation* rarely manifest clinically, due to no loss of DNA segment **(Fig. 11.2)**.

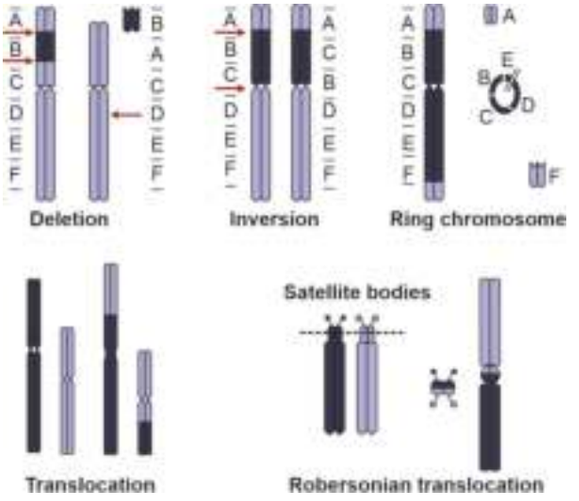

Fig. 11.2: Common structural abnormalities of chromosomes.

Robertsonian translocation is a specific translocation defect involving fusion of two acrocentric chromosomes near their centromere with loss of short arms, leading to reduction in total chromosomal numbers, (e.g. 45). Though the short arms of acrocentric chromosomes have no known function and carriers of Robertsonian translocations are phenotypically normal, they are at-risk for abortions.

Microdeletions, i.e. deletions, which are not visible on routine karyotyping and need special prophase studies for diagnosis, are being increasing recognized in association with various genetic disorders, e.g. Prader-Willi syndrome, William syndrome, Alagille syndrome, etc. Some important chromosomal disorders have been discussed in Ch 11.3.

Loss or gain of smaller regions of a chromosome, known as *copy number variations* (CNV), usually involve more than one gene and are implicated in many human diseases.

TABLE 11.2: Glossary of chromosomal abnormalities

Normal karyotypes
- ***Haploidy:*** Cells with 23 chromosomes, e.g., germ cells
- ***Diploidy:*** Cells with 46 chromosomes, e.g. somatic cells

Numerical abnormalities
- ***Euploidy:*** Number of chromosomes in multiple of haploidy (46, 69,...)
- ***Polyploidy:*** Euploidy with chromosomal numbers > diploidy (69, 92,..)
- ***Aneuploidy:*** Number of chromosomes not in multiples of haploidy.
- ***Trisomy:*** Presence of extra chromosome (47 XY/XX, Down syndrome)
- ***Monosomy:*** Absence of one chromosome (45 XO, Turner syndrome)

Structural abnormalities*:
- ***Deletion:*** Loss of a chromosome segment (Cri du chat syndrome)
- ***Translocation:*** Inter-chromosome transfer of DNA segment
- ***Inversion:*** Detachment of DNA segment > re-attachment in reverse order

*also see Fig. 11.2

2. Single Gene (Monogenic) Disorders

As stated earlier, each gene has an analogous allele at the identical location on other chromosome of the pair affecting same biological characteristics, but may or may not be identical (*homozygous vs heterozygous).*

In heterozygous state, generally one gene of the allelic pair determines biological activity (*dominant* gene), while other remains suppressed (*recessive* gene) and manifests only in absence of dominant allele. Thus, disorders encoded on dominant genes manifest even in a heterozygous state, while disorders of recessive genes

are asymptomatic in heterozygous state (suppressed by normal allele) and manifests only in homozygous state.

As the genes present on X-chromosome of a male (XY) do not have their corresponding allele *(hemizygous state)*, an X-linked recessive gene manifests only in males and remains suppressed in heterozygous females (XX).

Thus, single gene disorders may be broadly divided into 4 categories—(a) autosomal dominant, (b) autosomal recessive, (c) X-linked recessive, and (d) X-linked dominant disorders. *Y-linked genetic abnormalities* are rare and present with minor phenotype features in males, inherited from fathers, e.g. hairy pinna, frontal baldness, webbed toes, porcupine skin, etc.

Autosomal dominant (AD) disorders, i.e. defects encoded on the dominant gene on autosomal chromosome, are characterized by following features **(Fig. 11.3)**:

- *Clinical manifestation in heterozygous state,* as the defect is encoded on the dominant gene of the pair. Homozygous states are rare for ADDs and present with more severe disease.
- *No silent carriers,* as all genetically abnormal members of the family manifest clinically, unless the gene has not manifested due to incomplete penetrance.
- *Vertical inheritance,* i.e. history of similar disease in one of the parents (or previous generations), unless the genetic error is a new *de novo* mutation.
- *Usual risk of recurrence* during each pregnancy being 50%, when one parent is heterozygous and another is normal. In rare cases, it may be even higher if one parent is homozygous (100%) or both parents are heterozygous (75%).
- *Both sexes are equally affected,* as the defective gene is present on the autosomes.
- *Most ADDs are non-lethal* and hence, more common than recessive defects due to survival of affected individuals till reproductive age.

Common examples of ADD are achondroplasia, neurofibromatosis, Marfan syndrome, hereditary spherocytosis, etc.

Autosomal recessive (AR) disorders, i.e. defects encoded on the recessive gene of autosomal chromosome, are characterized by following features **(Fig. 11.4)**.

- *Clinical manifestations only in homozygous state*, due to absence of corresponding dominant gene to suppress mutant gene activity.
- *Silent carrier state in heterozygous individuals*, due to suppression of abnormal gene by corresponding dominant gene. However, some carriers may have borderline abnormalities.
- *Horizontal inheritance*, i.e. all members of same generation are genetically affected, when a heterozygous carrier mates with another heterozygous carrier. However, some of them manifest with disease (if homozygous), while rest become carriers (if heterozygous). Parental history of similar disease is absent in these cases, who are heterozygous carriers.
- *Usual risk of recurrence* in subsequent pregnancy is 25% for homozygous disease and 50% for heterozygous carriers, if both parents are carriers. All children of a homozygous patient (very rare) are carriers, if the other partner is normal.
- *Consanguinity* is an important risk factor for ARDs, as the members of same family tree are more likely to be heterozygous carriers, than the general population.
- *Both sexes are equally affected,* as the defective gene is present on the autosomes.
- ARDs are frequently lethal and hence, relatively rare due to unlikely survival of a diseased case till reproductive age.

Common examples of ARDs are severe forms of inborn errors of metabolisms, hemoglobinopathies and skeletal dysplasias, etc.

X-linked recessive (XLR) disorders denote a defect of recessive gene located on X chromosome, characterized by following features **(Fig. 11.5)**:

- *Clinical manifestations only in males* (XY), due to absence of corresponding dominant gene to suppress the abnormal recessive gene. Females (XX) are not affected due to presence of normal dominant gene, *except* in very rare instances of 45, X genotype (Turner syndrome), X autosome translocation, skewed X inactivation, fresh mutations or a diseased male mating a carrier female. However, carrier females may have mild and silent biochemical defects, e.g. low factor VIII activity in hemophilia.

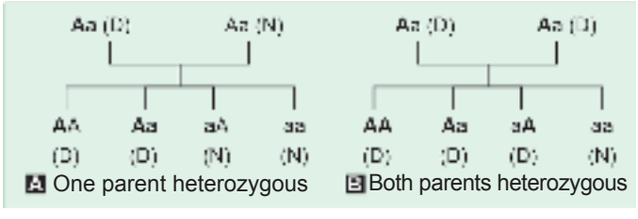

Fig. 11.3: Autosomal dominant inheritance.
Bold 'A' denotes abnormal dominant gene
N: normal, **D:** diseased

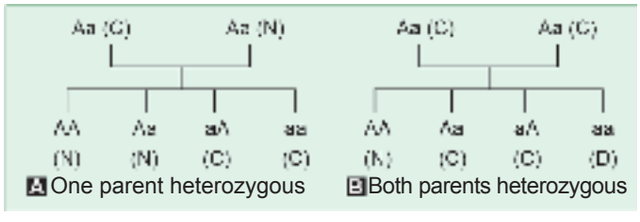

Fig. 11.4: Autosomal recessive inheritance.
Bold 'a' denotes abnormal recessive gene
N: normal; **D:** diseased; **C:** carrier

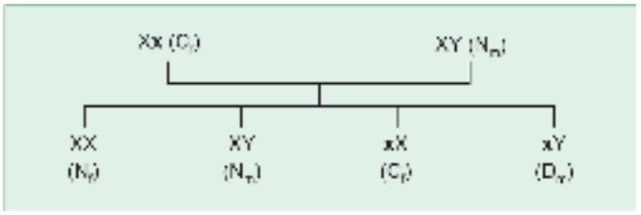

Fig. 11.5: **X-linked recessive inheritance.**
N: normal, **D:** diseased, **C:** carrier
Genes in bold letters denote abnormal gene, subscripted letters m and f denote male and female.

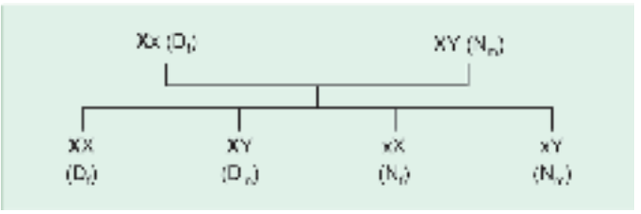

Fig. 11.6: **X-linked dominant inheritance.**
N: normal; **D:** diseased
Genes in bold letters denote abnormal gene, subscripted letters m and f denote male and female.

- *Carrier state only in females* (XX), as males are always affected by disease.
- *Oblique transmission*, i.e. only males on maternal side, (e.g. maternal uncles) are affected with disease, while mother is an asymptomatic carrier and father is normal.
- *Usual risk of recurrence* during next pregnancy is 50% for disease in males or carrier state in females, when mother is a carrier.

Common examples of XLRs are hemophilia, Duchenne muscular dystrophy, color blindness, G6PD deficiency, etc.

X-linked dominant (XDD) disorders are uncommon and characterized by **(Fig. 11.6)**:

- *Clinical manifestations in both sexes*, as females are also affected due to dominant nature of abnormal gene.
- *Risk of recurrence* is 50% if mother in heterozygous and father is normal. However, all female offsprings of a hemizygous father are affected.
- *Disease tends to be less severe in females*? due to modifying effect of corresponding normal allele, thus creating excess of females in XLD families.
- As males are more severely affected, defective gene is usually acquired from maternal side.

Common examples of XLDs are familial hypophosphatemic rickets, incontinentia pigmenti, orofacial digital syndrome, nephrogenic diabetes, etc.

3. Polygenic and Multifactorial Disorders

Often confused together, these two terms have different connotations. While *polygenic disorders* represent a "defect regulated by additive or interactive effect of two or more genes", *multifactorial disorders* refer to a "*genetically determined susceptibility of certain individuals to various environmental factors*". Various normal human traits, e.g. height, as well as abnormal disorders are multifactorial in origin. In these cases, contribution of genes is termed *heritability*.

While exact genetic error in most MFDs is usually not clear, some have strong association with certain specific HLA types, e.g. diabetes (DR3/4), spondyloarthropathy (B27), etc.

TABLE 11.3: Recurrence risk in multifactorial disorders

	General incidence (1000 live births)	*Recurrence risk* (%)*
Neural tube defects	4–5	5%
Cardiac malformations	6–8	3–4%
Cleft lip and palate	2	4–5%
Cleft palate alone	0.5	2–6%
Pyloric stenosis	2–3	3%
Cong. talipes equinovarus	3–4	2–8%
Cong. dislocation of hip	3–4	3–4%
Hirschsprung disease	0.1	6%

*If previous sibling is affected, with normal parents.

Risk of recurrence (RR) in MFDs, in absence of well-defined genetic basis, is usually estimated on the basis of epidemiological observations **(Table 11.3)**. Some general observations are as follows:

- RR in most MFDs is ~2–10% among first-degree relatives, and gradually declines in more distant relatives.
- RR rises by 2–3 folds, when more than one family members, e.g. one parent and one sibling or two siblings are affected (d/d single gene disorders, where it is same for each pregnancy).
- RR is higher in common and severe disorders, as compared to rare or benign defects.
- In disorders with sex-predilection, RR is higher if the index case belongs to rarely affected sex, e.g. in Infantile hypertrophic pyloric stenosis, which is common in males, RR is higher for offspring of an affected mother than of affected father.
- Unlike single gene defects, presence of similar MFD disorder in identical twins (concordance) is never 100%, usually being 21–63%.

4. Mitochondrial Disorders

Mitochondria contain ~16,000 bps of DNA, arranged in small circular segments (mitochondrial chromosomes). Mutations in mitochondrial genome are responsible for many genetic disorders, e.g. Leber hereditary optic neuropathy, MELAS (*M*itochondrial myopathy

*E*ncephalopathy, *L*actic acidosis and *S*troke), Leigh syndrome and MERRF (myoclonic epilepsy with ragged-red fibers). Mitochondrial disorders are characterized by:

- Involvement of specific tissues, e.g. brain, muscles and eyes.
- Exclusive inheritance from mothers, as sperms do not contain mitochondrial component. However unlike X-linked disorders, offsprings of both sexes are affected in these disorders.

5. Non-traditional Modes of Inheritance

Non-traditional modes of inheritance include some genetic traits, which are not determined by an equal genetic contribution from both parents or do not follow conventional modes of inheritance discussed earlier. Some important disorders of this nature are as follows:

Uniparental disomy (UPD) denotes a mode of inheritance in which *both chromosomes (or part of a chromosome) of a pair are inherited from same parent*. Most important effect of UPD may be increased risk of manifesting autosomal recessive disorders, due to transfer of two identical chromosomes carrying mutant genes from a heterozygous parent. UPD has been observed in many recessive disorders, e.g. cystic fibrosis or other defects, e.g. Prader-Willi syndrome and Russell-Silver syndrome.

Genomic imprinting refers to the *differences in the phenotype expression of a genetic defect, depending on the parent of origin* for implicated gene/chromosome. For example, deletion of paternally-derived 15th chromosome presents with *Prader-Willi syndrome*, while similar deletion of maternal-derived chromosome manifests as *Angelman syndrome*.

Mosaicism refers to an *individual with two different cell lines*, derived from a single zygote (mitotic non-disjunction). Over 2% of conceptions are estimated to have mosaic chromosomal abnormality in first trimester. Mosaic defects tend to be less severe and often allow the survival in otherwise lethal chromosomal defects due to presence of normal cell lines. Mosaicism may be divided into:

- *Chromosomal mosaicism*, e.g. Down syndrome (46/47), Turner syndrome (45,X/46XX);
- *Single gene mosaicism*, limited to certain genes, e.g. McCune-Albright syndrome, and
- *Germ-line mosaicism*, i.e. presence of mosaicism in germ cells. Unlike other types, germ-line mosaicism is inherited from parents and hence, may affect more than one offspring of mosaic parents, e.g. in Duchenne muscular dystrophy or osteogenesis imperfecta.

Chimerism refers to an individual with at least two or more cell lines, often originating from fusion of many different zygotes (d/d Mosaicism with single zygote).

6. Somatic Cell Disorders

The term '*somatic cell disorders*' refers to a new genetic mutation during mitotic cell division in the somatic cells, after differentiation of gonads. These mutations are limited to a single cell line and *not transmitted* to the next generation. Although each individual is likely to have many somatic mutations, most of them are silent and never detected. Two important examples of somatic mutations are *cancers* due to mutation in oncogenes, and *autoimmune disorders* due to mutation in genes regulating T-cell selection.

11.3 CHROMOSOMAL DISORDERS

Chromosomal abnormalities are present in ~0.4% of live births and ~50–60% of aborted fetus and include numerical as well as structural abnormalities. These abnormalities may be inherited from parents or arise *de novo* during gametogenesis.

When to suspect? Unlike singe gene disorders, Chromosomal disorders do not follow a specific pattern of inheritance and hence, family history is of limited significance in diagnosis. Physical dysmorphism is the hallmark of most chromosomal disorders, though **Table 11.4** enlists some common indicators of chromosomal disorders. Diagnosis is often based on constellation of clinical features many good databases are available to assist in the search for diagnostic possibilities.

Laboratory diagnosis of chromosomal disorders includes *study of chromosomal number and morphology*, using following methods:

- **Conventional karyotyping** may be performed on any living cells, e.g. lymphocytes, biopsies, aspirates, etc. or even the chorionic villi and amniotic fluid for prenatal diagnosis. Since the chromosomal profile is best appreciable during metaphase of mitotic division, karyotyping involves cell cultures to stimulate the mitotic division, arrest the division in metaphase by adding *colchicine*. dispersing these multiplying chromosomes by bathing the sample in hypotonic solution and then Staining with conventional stains, e.g. G-banding (Giemsa stain). In these stained slides, each chromosome is identified under microscope due to its unique light and dark banding patterns.

TABLE 11.4: Clinical indicators of chromosomal disorders

- **Family history of…**
  - Similar morphology/disease with unexplained etiology
  - Recurrent fetal or neonatal deaths or malformations
- **Physical characteristics**
  - External dysmorphic features
  - Multiple congenital malformations
  - Developmental delay/Intellectual disability
  - Ambiguous genitalia or sexual infantilism
  - Abnormal stature or deformities
  - Unusual cancers
- **Prenatal biochemical/USG abnormalities**
  - Abnormal USG
  - Abnormal biochemical markers

Conventional karyotyping require long time (2–3 weeks) for results and can identify numerical and structural chromosomal abnormalities, but only up to 5 Mb resolution.

- **Molecular cytogenetic studies,** e.g. Fluorescent *in situ* hybridization (FISH), quantitative Polymerase chain reaction (qPCR) and Multiplex ligation dependent probe amplification (MLPA) use target-specific fluorescent probes or markers against the suspected chromosome/s or regions. Results are available rapidly within 24 hours *but only* for the defect/s in that specific chromosome/s or regions. These tests are very useful where clinical suspicion limits the diagnostic possibilities, e.g. identification of aneuploidies for prenatal diagnosis and microdeletions.
- **Chromosomal microarray** has revolutionized the diagnosis of chromosomal disorders, based on the principle of complementary DNA hybridization to screen entire genome for differences from the known pattern, termed as copy number variations (CNVs), i.e. deletions or duplications. This test does not require living cell, results are available in few days and defects can be identified with a fine resolution of as low as 10–20 kb. However, microarray does not detect balanced translocations which do not alter CNVs and point mutations, deletions or duplications at the single gene level.

Chromosomal microarray is useful when there is a need to screen for many defects due to lack of a specific genetic diagnosis, e.g. unexplained intellectual disability, autistic spectrum disorders and multiple congenital anomalies.

Barr body (BB): In females, one of the two X chromosomes is randomly inactivated during early embryogenesis *(Lyon hypothesis)*, which may be seen as a clump of heterochromatin adjacent to the nuclear membrane (termed *Barr body)*. Males have only one X chromosome and hence no Barr body. Thus, the *number of BB is one less than the number of X chromosomes*. Detection of a Barr body in buccal smear is a quick method to identify the genetic sex in ambiguous genitalia (Female: one BB, Male: no BB) *or* disorders with abnormal X numbers, e.g. Turner syndrome (45 XO; no BB), 47 XXY female (2 BB), etc. However, these results are often misleading and no longer used in practice.

Some common chromosomal disorders are discussed as follows:

11.3.1 DOWN SYNDROME

Down syndrome (DS) is the commonest chromosomal aneuploidy in live-births, characterized by a typical phenotype and triplicate copy of entire chromosome 21 or its critical segment (DCR).

Incidence of DS in general population is ~1:600–800 live births, though the true incidence is much higher as ~50% of affected conceptions are spontaneously aborted. *Advanced maternal age is the most important risk factor for DS*, with an estimated risk of ~1:1000 below 30 years, ~1:350 by 35 years and ~1:100 after 40 years.

Cytogenetically, DS may be divided into two types- (a) *regular trisomy (~95%)*, i.e. presence of entire extra chromosome (47,XX/XY,+21); (b) *translocations (~5%)*, i.e. presence of 3 copies of DCR, but with normal chromosomal number (46, XX/XY).

- ***Regular trisomy*** is the commonest cause of DS in children born to elderly mothers, due to non-disjunction of 21st chromosome during meiotic phase in 94% cases or during mitotic phase in 1%. *In 95% cases of regular trisomy, the extra chromosome is derived from mother.*

  Non-disjunction in mitotic phase leads to *mosaicism*, in <1% cases witth presence of two different cell lines, one normal and another with trisomy.
- ***Translocations,*** i.e. the transfer of additional DCR *by transfer* on other acrocentric chromosomes (Robertsonian translocation), e.g. 14, 15, or 13 (usually t14;21), may arise *de novo* or inherited from a balanced carrier parent. Most are maternally inherited and only 20% are paternal. Maternal age is irrelevant and *most cases of DS born to younger mothers are translocations.*

Clinical phenotype of DS spans from presence of a few dysmorphic features to full-blown picture including developmental delay, hypotonia and systemic defects **(Fig. 11.7)**.

Common systemic problems present since birth include congenital heart diseases in ~40% (commonest being atrioventricular septal defect), gastrointestinal malformation, e.g. duodenal atresia in ~12%, hypothyroidism in ~15–50% and hearing defects in ~40–60%, while some others may arise after few years, e.g. atlanto-axial joint instability in ~10–30% and leukemia or other lymphoprolierative disorders in later life **(Table 11.5)**.

Fig. 11.7: Down syndrome: Facial appearance and simian crease (Inset).

TABLE 11.5: Clinical features in Down syndrome

- **External dysmorphism**
  - **Head:** Brachycephaly or flat occiput, microcephaly, Delayed closure of fontanels
  - **Eyes:** Upward slanting palpebral fissures, hypertelorism, Epicanthic folds, brushfield spots, cataract, refractive errors
  - **Nose:** Small and depressed nasal bridge, flat face
  - **Ears:** Small/dysplastic ears, deafness
  - **Oral cavity:** Dental hypoplasia, furrowed protruding tongue, high-arched palate
  - **Neck:** Short neck** with loose posterior folds in infancy
  - **Hands/feet:** Short/broad hands, clinodactyly**, sandal
  - gap (↑ gap between 1st and 2nd toe)
  - **Dermatoglyphics:** Simian crease** and others*, plantar (Kennedy) crease between 1st and 2nd toe
  - **Skin:** Dry, hyperkeratotic skin, fine sparse hairs, Cutis marmorata
  - **Genitals:** Cryptorchidism, micropenis
- **Generalized hypotonia with hyperextensible joints** hypotonia**, poor Moro's reflex**, hyper-extensible joints**
- **Developmental delay**
- **Systemic abnormalities**
  - **CVS:** Endocardial cushion defects, other CHDs
  - **GIT:** Obstructive lesions, e.g. duodenal atresia, Imperforate anus, Hirschsprung disease
  - **Respiratory:** Obstructive sleep apnea syndrome, hypoplastic lung, pulmonary hypertension
  - **Endocrinal:** Cong hypothyroidism, short stature, Infertility
  - **Hematological:** Leukemia, leukamoid reactions
  - **Skeletal:** Hypoplastic pelvis**, atlanto-axial instability
  - **Others:** Visual errors, deafness

*wide 'ATD' angle, distal triradius, ulnar loop ridge patterns
included in ***Halls criteria* for Down syndrome

TABLE 11.6: Periodic screening in Down syndrome

Karyotyping	*Birth/first contact*
Growth assessment	0, 6 mo, then... Annually till 18 years
Hearing assessment	0, 6 mo, 18–24 months, then... Annually till 6 years, then alternate year till 18 years
Eye evaluation	Birth, 2,4,6 yr, then.. Alternate years till 18 years
Thyroid profile	0, 6 ,12 mo, then annually every year
ECG/ECHO	Birth/ First contact
Dental evaluation	Annually from 1 year onwards
Complete blood count	0, 1 year then annually till 5 years

TABLE 11.7: Recurrence risk for Down syndrome

Normal parental karyotype
- Maternal age <35 years 1%
- Maternal age >35 years 1% more than age-related risk

Abnormal parental karyotype *(balanced translocation)*
- Mother as a carrier 10–15%
- Father as a carrier 5%
- T 21:21 (either parent) 100%

Despite developmental delay, these babies are friendly, playful and enjoy music. Motor development is slower than social development due to hypotonia, which tends to improve with age.

While many cases survive till adulthood and lead relatively independent life after learning the self-help skills, ~50% die in early childhood or need recurrent hospitalizations due to congenital heart diseases and recurrent aspiration (palatopharyngeal incoordination).

Diagnosis is largely clinical, though karyotyping is indicated in all cases to confirm the diagnosis, mode of inheritance and genetic counseling.

Management aims to: (a) improve the quality of life, (b) detect and treat systemic conditions, and (c) genetic counseling; and includes:

- *Confirmation of diagnosis* by karyotyping. If it is due to translocation, cytogenetic studies of parents are also necessary to detect balanced carriers and assess the risk for next conception.
- *Screening for systemic abnormalities*, e.g. congenital heart diseases, hypothyroidism and hearing/vision defects is essential at birth and then periodically, as many defects become apparent only in later life. IAP has recommended a time schedule for periodic follow-up for important medical issues till 18 years of age in all cases of DS **(Table 11.6)**.
- *General care* to ensure adequate nutrition, immunization, and growth and development monitoring.
- *Interventional programs*, e.g. physiotherapy, occupational therapy and self-help learning to achieve maximum functional independence.
- *Psychological support* to family.
- *Medical therapies*, i.e. megavitamins, selenium, piracetam, dimethyl sulfoxide, etc. have been tried in DS but with no proven value. However, associated illnesses, e.g. hypothyroidism should be promptly treated. Surgical intervention is indicated for major structural malformations. Cosmetic surgery for facial dysmorphism is justifiable in selected cases to increase social acceptance.

Genetic counseling is the most important component of management in DS and involves:

- **Assessment of recurrence risk** in future pregnancy: Recurrence risk for Down syndrome varies with maternal age and parental cytogenetic profile **(Table 11.7)**.
- **Prenatal screening** based on biochemical and USG markers **(Table 11.8)** is indicated in high-risk mothers, e.g. advanced age, previous affected child and abnormal parental karyotype, as follows:
  - ***First trimester screening*** (11–13 weeks) usually rests on: (i) reduced Pregnancy associated plasma

TABLE 11.8: Prenatal screening of Down syndrome

Screening tests	*Sensitivity*
First trimester screening (11–13 wk)	
• NT + Double marker test *(Serum free β-hCG and PAPP-A)*	85–95%
• NT + Double marker test + other USG markers*	93–96%
Second trimester screening (15–22 wk)	
• Triple marker test *(Serum AFP, free β-hCG, uE3)*	65–70%
• Quadruple marker test: *(Serum AFP, free β-hCG, uE3, inhibin A)*	70–75%
Confirmatory cytogenetic tests *(QF-PCR, Karyotype or FISH)*	
Chorionic villous sampling (11–13 weeks)	
Amniocentesis (17–23 weeks)	
Chordocentesis (>18 weeks)	

NT: Nuchal translucency; **hCG:** Human chorionic gonadotrophin; **PAPP-A:** Pregnancy-associated plasma protein-A; **AFP:** Alpha fetoprotein; **uE_3:** Unconjugated estriol; **QF-PCR:** Quantitative - fluorescent polymerase chain reaction
* See text

protein-A (PAPP-A) levels, (ii) elevated human chorionic gonadotropin (HCG) levels and (iii) increased nuchal thickness > 4 mm (echo-free space between skin and dorsal cervical spine).

Non-invasive prenatal screening (NIPS) is a new screening test in high-risk cases to analyse free fetal DNA in maternal plasma at ~10th week of gestation. It can detect aneuploidies of chromosome 21 with 99% sensitivity but false-positive results are possible and must be confirmed with cytogenetic studies.

– ***Second trimester screening*** (14–16 weeks) involves triple/quadruple marker test and includes presence of a combination of biochemical abnormalities in mother: (i) reduced-fetoproteins levels, (ii) reduced unconjugated estradiol levels, (iii) elevated human chorionic gonadotropin levels and (iv) increased inhibin levels in *Quadruple marker test*. A positive test indicates >50% risk of DS. Presence of certain USG abnormalities, e.g. heart disease or duodenal atresia also indicate need to exclude DS.

Important prenatal USG markers of DS include (*Two or more of following*): (a) increased nuchal translucency, (b) absent or hypoplastic nasal bone, (c) presence of soft markers like pyelectasis, echogenic bowel, echogenic intracardiac focus, single umbilical artery, choroid plexus cyst, short femur, etc., (d) structural abnormalities, e.g. duodenal atresia, cardiac defect, and (e) adjunct features like clinodactyly.

- **Confirmation of prenatal diagnosis,** by cytogenetic studies on suitable antenatal samples is possible in high-risk cases as early as 11–13 weeks by chorionic villous sampling, 17–23 weeks by amniocentesis and 18 weeks on cordocentesis. While conventional karyotyping takes ~2 weeks, PCR-based tests are available to give results in 2–3 days.
- **Parental counseling:** DS is a shattering diagnosis for parents and they should be informed as soon as possible after the confirmation in simple terms about: (a) confirmation of diagnosis, (b) possibilities of associated problems in present and in future, (c) need for regular follow-up to detect and mange these problems, (d) expected level and pace of development and achievement of life-skills, (e) risk of recurrence and options for prenatal diagnosis during next conception.

  They must also be counselled about immediate risks for life due to congenital anomalies. If any, morbidities which can arise in future and precautions required to minimize them. It needs to be emphasized that most cases of DS are trainable and can live near normal adult life with family support. Parents must be answered truthfully but compassionately for their apprehensions and may also be connected to support groups. Issues, e.g. schooling, menstrual hygiene etc may be discussed in future dates.

Other important somatic chromosomal disorders are as follows:

Trisomy 18 (Edward syndrome) is seen in ~1:6000 births, characterized by low birth weight, microcephaly, rocker-bottom feet, joint contractures/deformities overlapping fingers, developmental delay and cardiac/renal malformations. 95% of these cases die in infancy.

Trisomy 13 (Patau syndrome) is seen in ~1:10,000 births, characterized by *multiple midline defects*, e.g. facial defects (hypotelorism, bulbous nose, cleft palate, deformed ears, microphthalmia), cerebral malformations (microcephaly, encephalocele or holoprosencephaly), chest deformities (hypoplastic ribs, congenital heart diseases) and genital abnormalities (hypospadias). Polydactyly with overlapping fingers and visceral malformations are common and most cases die soon after birth.

Cri-du-chat syndrome, i.e. *deletion of short arm of 5th chromosome* (5p-), is characterized by typical cat-like cry, hypotonia, microcephaly with moon-like facies and mental retardation.

Microdeletion syndrome are characterized by multiple and small chromosomal deletions, missed on routine karyotyping studies.

Many microdeletion syndromes are being identified with newer diagnostic methods, commonest being *William syndrome* (typical *elfin* facies with supravalvular aortic stenosis), *Prader-Willi syndrome* (obesity, short stature, hypotonia), *Rubinstein-Taybi syndrome* (microcephaly, beaked nose with low philtrum, broad and long thumbs/toes), *DiGeorge syndrome* (first brachial

arch defects, e.g. thymus aplasia, hypocalcemia due to hypoparathyroidism, ear defects and congenital heart diseases) and *Alagille syndrome* (intrahepatic biliary atresia).

Chromosomal breakage syndromes: Some chromosome sites are known to show abnormal tendency for separation, breakage or attenuation, either spontaneously or under environmental stress, e.g. UV radiations (*Fragile sites)*. Many genetic disorders have been identified with fragile chromosomes, e.g. *Fanconi anemia*, *Bloom syndrome* (skin malignancies with mental retardation), *ataxia telangiectasia*, etc., as well as higher risk of malignancies.

11.3.2 TURNER SYNDROME

Turner syndrome is the commonest sex chromosome disorder *in females*, characterized by a spectrum of phenotype abnormalities and complete or partial absence of one X chromosome.

Incidence of Turner syndrome in female live-births is ~ 1:2500, though the turner genotype (45, XO) is present in 1–2% of conceptions, of which 95% are spontaneously aborted in first trimester. It is a sporadic defect with *negligible risk of recurrence* and maternal age is not a risk factor.

Cytogenetically, Turner syndrome may be divided into- (a) *classical karyotype* (50%), i.e. complete absence of one X chromosomes in all cell lines (45, XO), (b) *Mosaicism*, i.e. presence of two cell lines (45, XO/46, XX), and (c) rare structural defects, e.g. deletion of the p or q arm of X chromosome.

As the genes regulating ovarian function and growth (*SHOX* gene) are present on X chromosome, its complete absence leads to characteristic phenotype of Turner syndrome with short stature and gondal dysgenesis (streak ovaries). However, mosaic cases tend to have milder phenotype and better survival. Deletion of the *p* arm presents with typical phenotype, while deletion of the *q* arm is associated with only gonadal dysgenesis without somatic signs.

Clinical spectrum of Turner syndrome is highly variable **(Table 11.9)** and diagnosis is usually missed at birth. *Presence of lymphedema over dorsum of hands/feet and loose skin folds on the nape of neck are two important signs of Turner syndrome in newborns.*

Most cases present later with short stature, small triangular face, anomalous ears, short-webbed neck **(Fig. 11.8)**, wide chest, cubitus valgus with wide carrying angle at elbow, learning disabilities and delayed onset of puberty or menarche.

Congenital heart diseases, specially coarctation of aorta and renal anomalies are common. Hypothyroidism occurs in 15–30% adults with Turner syndrome. Stature may be normal in cases with mosaicism, who may present with secondary amenorrhea.

TABLE 11.9: Clinical features of Turner syndrome

- **Short stature**
- **External dysmorphism**
  - *Face:* Triangular facies, abnormal ears, cataracts
  - *Neck:* Short, webbed neck, low hairline
  - *Chest:* Broad chest with inter-nipple distance
  - *Limbs:* Carpel/pedal edema, cubitus valgus*
  - *Skin:* Nevi, recurrent keloids, dysplastic nails
- **Learning disabilities**
- **Systemic defects**
  - CVS: Coarctation of aorta, bicuspid aortic valve, AS
  - Renal: Horseshoe shaped or ectopic kidney
  - Skeletal: Scoliosis, made-lung deformity, CDH
  - Endocrine: Diabetes mellitus, obesity
- **Sexual infantilism (Gonadal dysgenesis)**
  - Delayed puberty
  - Amenorrhea/sterility

*Wide carrying angle at elbow >110°

Fig. 11.8: Turner syndrome: Webbed neck, widely spaced nipples and cubitus valgus.

Diagnosis is usually made during evaluation for short stature or delayed puberty in girls. Presence of streak ovaries on USG (and absence of germ cells on biopsy) is highly suggestive of Turner syndrome.

Diagnosis needs to be confirmed by karyotyping from peripheral lymphocytes or skin fibroblasts. *Buccal smear to detect absence of Barr body* is unreliable to exclude Turner syndrome, as it may fail to detect mosaicism and structural defects.

Other investigations are necessary in Turner syndrome to detect or exclude systemic defects, e.g. echocardiography, abdominal USG, audiometry and serum FSH/LH levels.

Prenatal diagnosis: As recurrence is extremely rare, prenatal diagnosis is indicated only in cases with some antenatal USG markers, e.g. cystic hygroma, lymphedema, hydrops fetalis, left-sided heart defects

and higher fetal heart rate, using cytogenetic studies from chorionic villus sampling or amniocentesis.

Management aims to maximize growth potential and early diagnosis/treatment of medical complications, with:

- *Parental counseling*, regarding its implications on growth and reproductive failure.
- *Periodic evaluation* for growth/development, hypertension, vision/hearing impairment, thyroid functions, etc.
- *Psychosocial support*.
- *Hormone replacement therapy* with growth hormone with/without an androgen, e.g. oxandrolone, is indicated when growth velocity falters and continued till bone age exceeds 14 years. In addition, Estrogen replacement with conjugated estrogen (0.3 mg/day) or ethinylestradiol (5–10 µg/day) is indicated at 14 years for 3–6 months, followed by cyclical estrogen/progesterone therapy to maintain menstrual cycle.
- *Prophylactic gonadectomy* in cases with streak gonads, to prevent risk of malignancy.
- *Assisted reproduction* options must be explained to an adult case, as infertility is almost universal.

Noonan syndrome, a variant of Turner syndrome is usually seen in males. These cases usually share some common phenotypic features with Turner syndrome, e.g. short stature and neck-webbing, hence sometimes referred in the past as "*male Turner syndrome*" or "*female pseudo Turner*". However, it is a single gene disorder affecting the RAS MAPK pathway (Rasopathy) and karyotype is essentially normal.

11.3.3 KLINEFELTER SYNDROME

Klinefelter syndrome is the commonest sex chromosome disorder *in males*, characterized by presence of extra X chromosome/s, though many of them remain undetected throughout the life.

Incidence of Klinefelter syndrome is ~1:1000 male live-births, being higher in children/adults with mental retardation or psychiatric problems.

Cytogenetically, commonest karyotype is presence of an extra X chromosome (47,XXY), due to meiotic nondisjunction. Advanced maternal age is a risk factor and extra X chromosome is of maternal origin in ~60% cases. Other variants include Mosaicism (46,XY/47,XXY) or more than one extra X (48, XXXY, 49,XXXXY, etc.).

Clinical spectrum is highly variable, with no well-defined somatic phenotype and many cases are indistinguishable from normal males. Mosaic individuals tend to have milder phenotype and better prognosis. Severity of the disorder increases with increasing number of X chromosomes.

TABLE 11.10: Features of Klinefelter syndrome

- **Abnormal development**
  - Delayed speech and language development
  - Scholastic failure and learning disabilities
- **Behavioral/psychological problems**
  - Shy/passive behavior with social isolation
  - Aggressive or anti-social behavior
- **Abnormal sexual functions**
  - Cryptorchidism, micropenis, hypospadias
  - Delayed puberty, poor virilization
  - Azoospermia and infertility
- **Somatic abnormalities**
  - Tall and thin stature (Eunuchoid features)
  - Cranio-facial abnormalities*

*mongoloid slant, epicanthic folds, large mouth, large/malformed ears and flat/wide nasal bridge

Most cases are normal in pre-pubertal period with delayed onset of puberty and gynecomastia being earliest presentation. Other important indicators include: (a) tall stature with long legs, (b) intellectual disability, (c) behavioral problems, and (d) abnormal sexual development, e.g. small testes, micropenis, etc. **(Table 11.10)**.

Diagnosis needs confirmation by cytogenetic studies, though presence of one or more *Barr bodies* (normally absent in males) have been used as a screening test.

Gonadal biopsy reveals reduction/absence of germ cells with hyalinization of seminiferous tubules. Gonadotropin levels (FSH/LH) are normal till early puberty, but subsequently, testosterone levels are lower and estradiol levels are higher than the age-related values.

Management includes: (a) early intervention programs for speech/language dysfunction and learning disabilities, (b) psychotherapy, and (c) hormone replacement therapy with testosterone enanthate, from 11–12 years onwards to facilitate virilization.

Other important sex chromosome disorders are:

47 XYY male, is a common (1:1,000 live births) but usually an asymptomatic chromosomal defect, with no striking phenotype abnormalities, except relatively tall stature and mild behavioral problems.

Fragile X syndrome is one of the commonest causes of mental retardation in males, characterized by presence of an abnormally fragile site on long arm of X chromosome (usually Xq27.3) due to unstable DNA sequence (allelic expansion of the trinucleotide sequence CGG located in the 5′ untranslated region of FMR1 gene). Typical phenotype includes: (a) macrosomia, i.e. large body size, (b) characteristic facies with long face, macrognathia and prominent ears, (c) macroorchidism, and (d) intellectual disability with stereotyped behavior and speech. Females are less severely affected than males, though present with premature ovarian failure.

11.4 EVALUATION OF GENETIC DISORDERS

All familial disorders are not necessarily genetically inherited (may be due to common environmental factors, e.g. malnutrition or infection) and similarly, all inherited disorders are not familial (may be due to new mutations).

Diagnostic evaluation for a genetic disorder is usually indicated on the basis of strong family history *or* clinical suspicion and aims to: (a) confirm the diagnosis in the index case, (b) detection of carrier state in parents/siblings of index case; and (c) prenatal diagnosis in a suspected high-risk fetus.

Elaborate laboratory investigations are indicated only in selected cases with strong possibility of a known or unknown genetic defect.

This section deals with three important steps in genetic diagnosis: (a) suspecting the genetic disease, (b) clinical evaluation in these cases; and (c) laboratory workup in selected cases.

Step I. Suspecting the genetic disease: Family history and unexplained clinical features **(Table 11.11)** are most important clues to a genetic disease, although note that:

- *A negative family history does not exclude genetic defect* and the index case may be the only affected member of family, as recurrence risk is only 25–50% in single gene disorders and even lesser in multifactorial disorders or new mutations.
- *A genetic defect may have variable expression*, ranging from typical textbook description to very mild disease or physical stigmata.
- *Similar phenotype may develop due to different genetic errors*, e.g. arachnodactyly is seen in Marfan syndrome as well as homocystinuria.

TABLE 11.11: Indicators of genetic disease

a. Family history of…
- Similar disease with unexplained etiology
- Known genetic defect or carrier state
- Recurrent fetal/neonatal deaths

b. Clinical indicators (unexplained)
- Critically sick newborn/infant
- Failure to thrive
- Persistent vomiting
- *Visceromegaly:* Hepatomegaly, etc.
- Developmental delay/Intellectual disability
- *Neurological:* Seizures, coma, hypotonia, etc.
- Respiratory distress
- *Hepatic:* Icterus, Gallstones
- *Hematological:* Cytopenia, clotting defects
- *Renal:* Chronic kidney disease, stones
- Hearing/vision defects
- *Dysmorphism:* Abnormal skin, hair, eyes, genitals
- Skeletal dysplasia

c. Biochemical abnormalties (unexplained)
- Abnormal urinary odor/color
- Intractable acidosis/ketosis
- Hyperammonimia
- Hypoglycemia or dyselectrolytemia

- *All genetic defects do not necessarily manifest at birth*-some may present even beyond childhood or may not present at all due to variable *penetrance*.

Step II. Clinical evaluation: Clinical evaluation in a suspected genetic disorder aims to confirm the diagnosis or the need for further laboratory work-up. Some important aspects of clinical evaluation in these cases are as follows:

- **Consanguinity**, i.e. mating between close-relatives, is a major risk factor for unmasking of autosomal recessive defect with risk being directly proportional to strength of consanguinity, as follows:
  - *First-degree consanguinity*, i.e. relationship between siblings or parent-offsprings.
  - *Second-degree consanguinity*, i.e. relationship between uncle-niece, aunt-nephew or step-siblings.
  - *Third-degree consanguinity*, i.e. relationship between first cousins.
- **Pedigree charting:** Pedigree charting is one of the most important tool to recognize genetic defects and their mode of inheritance, which requires careful history as well as examination of living relatives for at least *three* generations of index case (Proband or Propositus).

  Common symbols used for pedigree construction are given in **Fig. 11.9B**. By convention, all members of same generation (living or dead) are placed in one horizontal line, with male members on the left side. Each generation is also denoted by roman numerals on left side. **Fig. 11.9A** has given a sample pedigree of an autosomal recessive disorders
- **Constellation of clinical signs:** Genetic frequently present with a constellation of clinical features, rather than an isolated abnormality. Many disorders are identifiable by combination of these features (syndrome). **Table 11.12** enlists some useful pointers (handles) towards genetic disorders. For easier syndromic search, it is advisable to use an uncommon handle as starting point, as features, e.g. mental retardation, simian crease, failure to thrive, etc. are *too* non-specific to facilitate a single diagnosis.

  Various databases like *Online Mendelian Inheritance in Man* (OMIM) or *Phenomizer* can be used to conduct search.

Step III. Laboratory evaluation: Laboratory evaluation of genetic disorders is often costly and indicated only in selected cases with strong possibility of a these defects, with choice depending on the probable clinical diagnosis.

Diagnostic investigations in genetic disorders may be broadly divided into (a) *molecular genetic studies* for suspected genetic disorders, and (b) Biochemical *(enzymatic) studies* for suspected inborn errors of metabolism. In addition, some overlapping cases may also need cytogenetic studies to rule out chromosomal disorders, discussed in Ch 11.3.

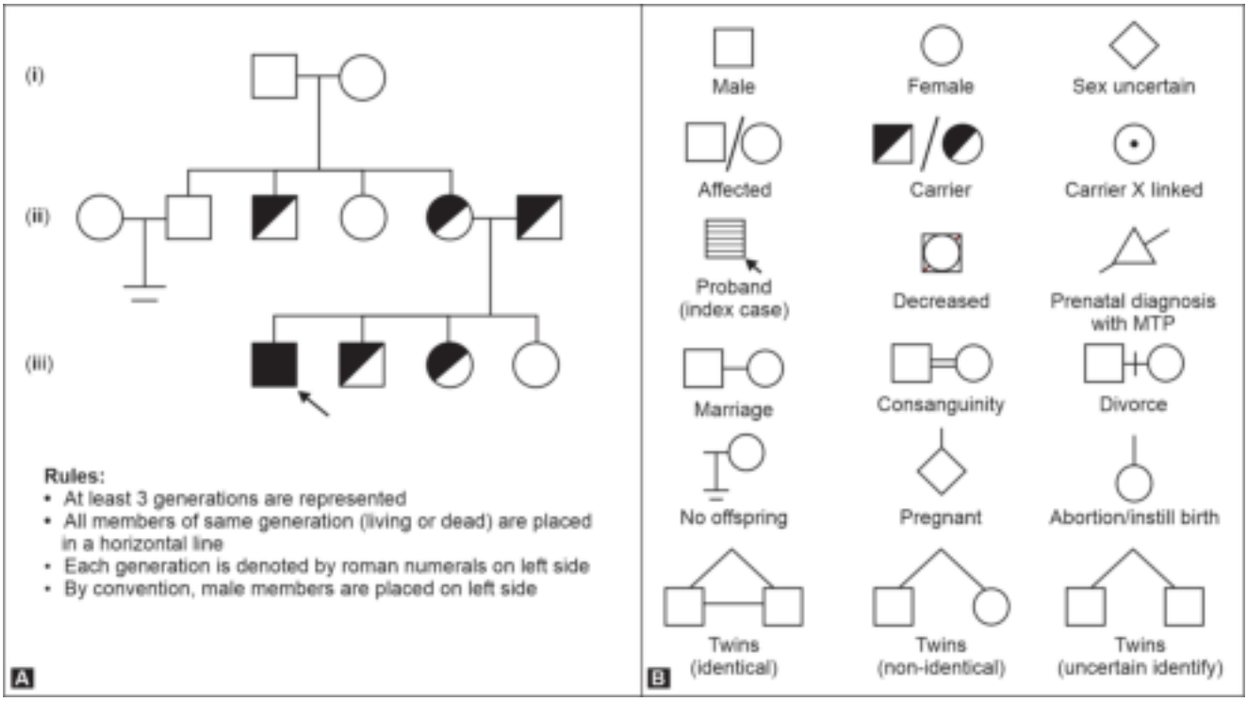

Fig. 11.9A and B: **Pedigree charting: (A) Representative pedigree chart (B) with commonly used symbols.**

TABLE 11.12: Suitable clinical handles (starting points) for genetic diagnosis

Dysmorphic features
- *Stature:* Tall/short/disproportionate stature
- *Head:* Microcephaly, craniosynostosis
- *Eyes:* Cataracts, coloboma, retinitis
- *Ears:* Deafness, deformed ear, preauricular tags
- *Mouth:* Cleft lip/palate, large tongue
- *Neck:* Webbing, masses
- *Limbs:* Poly/syndactyly, dermatoglyphics
- *Back:* Spina bifida
- *Genitals:* Ambiguous genitals, micropenis
- *Skin/hair:* Dyspigmented skin patch/hair

Systemic abnormalities
- Organomegaly, e.g. hepatosplenomegaly
- Major malformations, e.g. CHD, gut atresias
- Skeletal abnormalities

Biochemical abnormalities
- Abnormal urinary odor
- Acidosis, hyperammonimia
- Recurrent/persistent icterus, hypoglycemia

Molecular genetic testing for single/multiple gene defects involve study of the specific DNA sequence from a sample of blood or other body fluids/tissues. These tests are also valuable to detect carrier states for single gene disorders. Some common molecular genetic tests include:

- ***Amplification methods*** to clone the sequence of interest in a DNA fragment using polymerase chain reaction (PCR) and form multiple copies, which can then be examined by specific probes or primers. Results are available within few hours and commonly used for genetic studies when very small quantities of DNA are available as well as to detect viral/bacterial DNA in infectious disorders.

  Many variants of PCR tests are available at present including Real time PCR, Multiplex PCR, Nested PCR or Reverse transcriptase PCR (RT-PCR), the last one to amplify RNA.
- ***Hybridization methods*** using DNA probes tagged with radioactive or fluorescent markers, to attach to the complementary sequence in subject's DNA. These hybridized probes can be later detected by various methods, e.g. FISH, MPLA, southern blotting, etc.
- ***Sequencing methods*** to compare the sequence of whole or part of the DNA from patient with reference population to detect genetic alterations and include two common methods – Sanger sequencing and Next generation sequencing (NGS).

Next generation sequencing (NGS): Only 1% of human DNA is used for protein coding (Exons), the rest being in non-coding regions (Introns), though it may regulate functions of Exons. NGS has emerged as the most powerful tool for diagnosis of monogenic disorders, which includes: (a) *targeted panel testing* of selected regions, (b) *exome sequencing* of whole coding regions (ES), and (c) *whole genome sequencing* (WGS) of coding as well as non-coding regions.

NGS involves fragmentation of the DNA sample into multiple fragments followed by capture of selected or entire DNA fragment for sequencing. This sequence,

when compared with reference population, may reveal many differences (variants), which may or may not be of pathogenic significance and need correlation with clinical phenotypes for interpretation.

NGS is usually preferred test in cases with overlapping or probably new phenotypes, for which precise genetic defect is difficult to specify with multiple possibilities.

Biochemical studies are indirect but most frequently used methods to detect *genetic disorders* for which the actual enzymatic defect is known to cause the disease. These tests can be applied in the index case, prospective carrier or in the fetus for prenatal diagnosis and include: *(a) primary enzyme assays*, e.g. hexosaminidase-A in Tay-Sachs disease; *(b) non-enzymatic protein assays*, e.g. fVIII assay for hemophilia; *(c) secondary biochemical abnormality tests*, e.g. CPK levels for Duchenne muscular dystrophy or Hb electrophoresis in hemoglobinopathies.

Many biochemical tests, though not diagnostic of a specific genetic disorder or IEM *per se*, help in short-listing the differential diagnosis in these defects, e.g. hyperammonemia, acidosis, hypoglycemia, etc. Relevance of these tests in diagnosis of IEM has been discussed in chapter of IEM.

11.5 MANAGEMENT OF GENETIC DISORDERS

Management of genetic disorders includes three important components: (a) treatment of the index cases, (b) genetic counseling to prevent recurrence in subsequent pregnancy, (c) prenatal diagnosis for appropriate decision.

11.5.1 TREATMENT OF INDEX CASE

Genetic disorders cannot be cured and treatment is largely supportive, including physiotherapy, blood transfusions, e.g. haemolytic anemia, surgical treatment of malformations, incl. However, recent therapeutic advances in the management of these rare diseases have be able to prevent the severe morbidity or at least slow down the progression of disease, with following measures:

- **Dietary manipulations** to reduce the intake of substances which cannot be adequately metabolized in a genetic defect, specially if they are potentially toxic, e.g. removal of galactose (milk) from diet in galactosemia.
- **Enhancing urinary excretion** of toxic metabolites by drugs, e.g. sodium benzoate in urea cycle defects, penicillamine in Wilson disease or desferrioxamine in thalassemia.
- **Enzyme inducers** and coenzymes to augment deficient enzymes in certain defects, e.g. phenobarbitone for Crigler-Najjar syndrome. Desmopression in haemophilia. Administration of mega doses of vitamins have been successful in some defects to bypass enzymatic block, e.g. biotin in biotinidase deficiency, pyridoxine in homocystinuria
- **Enzyme replacement therapy (ERT)** is available for many lysosomal disorders at present, e.g. Gaucher disease, Niemann-Pick disease, Hurler syndrome and some other mucopolysaccharidoses, Pompe disease, Fabry disease, etc., though at a prohibit cost. Factor VIII therapy in hemophilia is another example of enzyme replacement therapy.
- **Avoidance of precipitating factors:** Symptoms of many IEMs are precipitated by prolonged fasting, heavy exercise, sun-exposure or exposure to certain drugs, e.g. primaquine in G6PD deficiency or Barbiturates in porphyria, which can be avoided.
- **Removal of disease organ,** e.g. splenectomy in hereditary spherocytosis of thyroidectomy in multiple endocrinal dysplasia.
- **RNA Modulators,** i.e. antisense oligonucleotides (ASO) therapy, e.g. Nusinersen (Spinal muscular dystrophy), Eteplirsen (Duchenne muscular dystrophy), etc.
- **Stem-cell transplant** is the ultimate therapy for many genetic defects, e.g. thalassemia major, Hurler syndrome and some primary immunodeficiencies. Liver transplant may be useful in many urea cycle defects.
- **Molecular targeted therapy** is available for certain disorders, e.g. Ivacaftor or Lumacaftor for cystic fibrosis, Nusinersen or risdiplam for spinal muscular atrophy and exon-skipping drugs for Duchenne muscular dystrophy and Imatinib for chronic myeloid leukemia.
- **Gene therapy** is possible for some disorders, e.g. SMA, Metachromatic leukodystrophy and some cancers, discussed as below.

Gene therapy aims '*to replace an identified abnormal gene with a normal gene*, i.e. *recombinant DNA, to modify or manipulate cell function and correct the genetic defect*.' It is emerging as an exciting option to cure many single gene defects and multifactorial disorders, e.g. cancers. However, medical and ethical issues support use of gene therapy only in rare and serious life-threatening disorders, for which no effective therapy are known.

Gene therapy involves: (a) isolation of recipient's plasmid, (b) selection of normal donor/recombinant gene for replacement from established gene libraries, (c) insertion of the normal gene into recipient's plasmid, (d) facilitating the multiplication of recombinant plasmid to yield multiple copies of new gene and (e) delivery of the recombinant DNA to the target cell nucleus. Direct insertion of a gene into cultured mammalian cells is also possible, if the candidate gene is introduced along with its promoter.

Depending on the type of recipient cell, gene therapy may be divided into: (a) *somatic cell therapy*, i.e. transfer of recombinant DNA into somatic cells, e.g. muscle cells

TABLE 11.13: Common disorders for gene therapy

- Spinal Muscular atrophy (Zolgensma)
- β-thalassemia (Zynteglo)
- Hemophilia A (Hemgenix)
- Retinal dystrophy (Luxturna)
- cerebral Adrenoleukodystrophy (Skysona)
- Adenosine deaminase deficiency (ADA)
- Alpha-1 antitrypsin deficiency (A1AT)
- Cystic fibrosis (CFTR)
- Familial hypercholesterolemia (LDL receptor)
- Gaucher's Disease (acid β glucosidase)
- Phenylketonuria (PAH)
- Neuroblastoma (IL-2)

in Duchenne muscular dystrophy or bone marrow for thalassemia; and (b) *germ-line therapy*, i.e. transfer of recombinant DNA into germ cells for transmission to future generations. Germ-line therapy, is considered as unethical for human use, though has been successfully adopted for obtaining α-glucosidase enzyme from rabbit milk for treatment of *Pompe's* disease.

Various *delivery systems* are used to insert donor gene into the recipient's plasmid including *physical methods*, e.g. gene-gun technology, *viral vectors*, e.g. retroviruses, adenoviruses and *non-viral vectors*, e.g. liposomes, DNA-ligand complexes and vaccines.

Gene therapy has shown promising results in many disorders and has been approved by USFDA for over 30 conditions **(Table 11.13)**.

11.5.2 GENETIC COUNSELING

Genetic counseling may be defined as *"a communication process between appropriately trained person/s and the parents/prospective parents, regarding the occurrence or the risk of occurrence of a genetic disorder in a family"*.

Aims: It aims to enable family members to:

- *Comprehend the medical facts* regarding genetic defect in the index case, e.g. diagnosis, probable course and available management,
- *Appreciate the hereditary aspects and risk of recurrence* in specified relatives,
- *Understand the options* to deal with the risk of recurrence,
- *Choose the appropriate course of action*, according to risk-estimates, family-goals, ethical and religious standards (and act accordingly),
- *Make the best possible adjustment* to the existing disorder or risk of recurrence.

Genetic counselling assists the family to make informed decision and should not be used as a forum to enforce the counselor's views and opinions.

Indications: Genetic counseling is usually advisable in settings with:

- Family history of a genetic disease or a carrier state in parents, offspring or close-relatives.
- Obstetrical history of recurrent abortions, stillbirths or neonatal deaths
- High-risk pregnancies for genetic disease, e.g. consanguinity or advanced parental age.
- Identified high-risk families during screening programs, e.g. biochemical/radiological screening for Down syndrome or population screening for hemoglobinopathies.

Prerequisites: It is essential to ensure that:

- Provisional diagnosis of the index case is established to calculate the expected risk of recurrence.
- Results of carrier screening are available, if possible.
- Counsellor is well-trained in communication skills and well-informed about current knowledge on probable diagnosis/differential diagnosis.
- Session is conducted in complete confidentiality and relaxed atmosphere to ensure adequate parental comprehension.

Components: Important components of genetic counseling include:

- *Assessing the comprehension* capacity and knowledge of cosult and (parents), regarding probable genetic defect/s.
- *Providing essential information about the specific problem* in comprehensible terms, specially related to its natural course, need for diagnostic procedures, cost and usefulness of therapeutic interventions and quality/span of life. Use of appropriate audiovisual aids, e.g. pedigree charts, facilitates parental understanding, who may also be provided with addresses of support groups and relevant books or websites.
- *Explaining the probable risk of recurrence*, in terms of percentages and fractions. While it is possible to provide exact risk estimates in single gene disorders, a range or magnitude of risk (high, low or negligible) should be clearly stated, based on the current knowledge, if the diagnosis is uncertain *or* precise risk is unknown, e.g. in chromosomal disorders.
- *Offering the options regarding future conceptions*, e.g. feasibility of preventive interventions, (e.g. folic acid supplementation in neural tube defects), prenatal diagnosis/therapy with costs and risks/benefits of procedures, and alternate options, e.g. termination of an affected fetus, gene therapy, assisted reproduction or adoption. These options should be explained in unbiased and non-directive manner, avoiding recommendation of a particular option. It is emphasized that counsellor merely facilitates the decision process by parents but should never take a decision on their behalf or suggest an option, even if pressurized to do so.
- *Follow-up visits* to allow parents enough time to accept/understand the problem and decide future course of action.

11.5.3 PRENATAL DIAGNOSIS

Prenatal diagnosis of a suspected genetic/hereditary disease or congenital malformation is an important component of genetic counseling, referral to suitable centers for delivery and further management, as well as to prepare the family for the expected or unexpected outcomes. Recent developments in understanding of human genome, molecular biology, fetal/gene therapy and assisted reproduction have further enhanced the value of prenatal diagnosis.

Indications for prenatal diagnosis usually include:

- Advanced maternal age (>35 years) at delivery
- Obstetric history of recurrent abortions/stillbirths or neonatal deaths
- History of a potentially genetic disease or malformation in previous child
- History of a genetic disease, carrier state or abnormal karyotype in parents
- Abnormal maternal serum markers during antenatal screening
- Antenatal history of exposure to potential teratogens, e.g. infections, drugs, irradiations, etc.
- Abnormal prenatal USG/anomaly scans.

Prerequisites: Prenatal diagnosis is a costly and time consuming procedure, with inherent risks of diagnostic interventions. Hence, it should be offered only in selected cases, when:

- Accurate diagnosis of index case is available and parents have been identified with abnormal carrier state or chromosomal abnormality,
- Estimated risk of recurrence is fairly high and expected fetal disorder is sufficiently severe, to justify the need and risk for prenatal diagnosis.
- Available prenatal diagnostic tests for suspected defect are fairly sensitive and specific.
- No satisfactory postnatal treatment is available for suspected defect *or* delayed diagnosis is likely to worsen the outcome.
- Option of pregnancy termination or fetal/gene therapy is acceptable to the couple in case of abnormal result.
- Family has made an informed decision to accept risks/benefits of such intervention and consented in writing.

Techniques: Prenatal diagnostic tests may be broadly divided into: (a) screening tests, and (b) specific diagnostic tests **(Table 11.6)**.

Screening tests are simple and cost-effective interventions to identify high-risk mothers in need of further investigations and should form the part of regular antenatal workup. Pre-conception carrier state for many recessive disorders may be identified by selected screening investigations in high-risk mothers, e.g. serum CPK levels for Duchenne muscular dystrophy, HbA_2 levels for thalassemia, etc. Important prenatal screening tests **(Table 11.14)** are as follows:

TABLE 11.14: Prenatal diagnostic tests

Maternal studies

- Prenatal USG studies
  - Level 1 and 2 anomaly scans
  - Early transvaginal scans
  - Late malformation scans
- Biochemical
  - Triple marker test
  - Quadruple marker test
- Non-invasive prenatal screening
- *Others:* TORCH screen, Hb electrophoresis

Fetal studies

- Cytogenetic and molecular diagnostic tests
  - Chorionic villous biopsy (~11–13 weeks)
  - Amniocentesis (~17–23 weeks)
  - Cordocentesis,(> 18 weeks)
- Biochemical enzyme assays
- *Others:* Fetoscopy, fetal echocardiography

- ***Prenatal ultrasonography*** is the most commonly used prenatal screening test to detect major/minor structural malformations *in utero*, as well as to assist in collection of samples for advanced cytogenetic studies.

  Routine transabdominal USG screening is recommended at 11–13 weeks (Level 1 anomaly scan) and again at 18–20 weeks (Level 2 anomaly scan) of gestation in all antenatal mothers. However, additional USGs are advised in high-risk pregnancies, as follows:

  Early transvaginal scans to detect markers of chromosomal defects, e.g. first trimester markers, e.g. cystic hygroma, hydrops fetalis, nuchal translucency, growth retardation and fetal heart rate abnormalities; and second trimester markers, e.g. nuchal thickening, echogenic bowel, short extremities, pyelectasis, intracardiac echogenic foci, brain ventriculomegaly, clinodactyly, etc.

  Late scans (20–24 week) to detect malformations, which may be missed on routine USG at 18–20 weeks, e.g. small bowel atresia, esophageal atresia, diaphragmatic hernia, renal tract anomalies and achondroplasia. Disorders, e.g. skeletal dysplasia may be identified, using intrauterine nomograms and growth curves on serial scans from second trimester onwards.

  3-D USG scans are also available to detect minor fetal malformations, e.g. cleft palate, single vertebral defects.
- ***Maternal biochemical markers:*** Conventional protocols for biochemical screening at 11–13 weeks gestation include *Triple marker test* at 11–13 weeks of gestation (α-fetoprotein, total or free β-human chorionic gondotropin and unconjugated estriol levels) and Quadruple marker test at 14–16 weeks (Triple markers + inhibin levels), to predict fetal chromosomal defect, e.g. Down syndrome (Ch 11.3.1).

- ***Non-invasive prenatal screening*** (NIPS) is a new screening test in high-risk cases to analyse free fetal DNA in maternal plasma at ~10th week of gestation. It can detect aneuploidies of chromosome 21 with 99% sensitivity but false-positive results are possible and must be confirmed with cytogenetic studies.

Specific genetic studies in fetus are indicated only in a selected subset of high-risk mothers, as identified on routine screening tests *or* with known risk of genetic disease. While most of them are expensive and require invasive sample collections with inherent risk of procedure, information obtained is often precise enough to confirm or exclude a suspected defect. These tests include karyotyping, molecular diagnosis and enzyme studies in fetal samples to confirm or exclude suspected genetic defect.

Choice of the method to collect these samples depends on the gestational age at the time of proposed prenatal diagnosis and usually include chorionic villous biopsy at ~11–13 weeks, amniocentesis at ~17–23 weeks and cordocentesis, at >18 weeks. Fetoscopy is most traumatic and rarely used, except to obtain samples of fetal tissues, e.g. liver or skin for enzymatic studies.

All these techniques except fetoscopy, are fairly safe in expert hands with estimated risk of fetal loss as 0.1–0.2%. Fetoscopy is associated with >5% risk of abortion. However, some fetomaternal hemorrhage is inevitable with these procedures and hence, administration of Rh immunoglobulin is indicated in all Rh –ve mothers taken up for these studies.

11.6 INBORN ERRORS OF METABOLISM

The term "Inborn errors of metabolism" refers to a broad group of *genetic defects with qualitative or quantitative deficiency in one or more enzymes or their co-factors, involved in synthesis, transport, storage, metabolism or degradation of various biochemical compounds in body*.

Consequently, these enzymatic defects may lead to: (a) deficiency of final metabolite product, (b) accumulation of proximal substrate in metabolic pathway, or (c) activation of alternate metabolic pathways with formation of abnormal metabolites.

More than 300 of such disorders are known, with an estimated incidence of 3–4/1000 births, though many of them are asymptomatic or never diagnosed. According to the predominant metabolic defect, these disorders may be broadly classified as disorders of: (a) amino acid metabolism, (b) fat metabolism, (c) carbohydrate metabolism, (d) nucleic acid metabolism, and (e) miscellaneous errors **(Table 11.15)**.

TABLE 11.15: Classification of inborn errors of metabolism (IEM)

- **Amino acid metabolism**
  - Aminoacidurias
  - Urea cycle defects
  - Organic acidemias
- **Carbohydrate metabolism**
  - Glycogen storage disorders (GSDs)
  - Galactosemia and fructose intolerance
  - IEMs with lactic acidosis
  - Glycoproteinoses
  - Mucopolysaccharoidoses (MPS)
- **Fat metabolism**
  - Mitochondrial fatty acid oxidation defects
  - Peroxisomal disorders
  - Lipoprotein metabolism/transport defects
  - Lipid storage disorders (lipidoses)
- **Nucleic acid metabolism**
  - Purine metabolism, e.g. Lesch-Nyhan syndrome
  - Pyrimidine metabolism, e.g. Orotic aciduria
  - Gout
- **Miscellaneous disorders**
  - Heme metabolism, e.g. porphyria
  - Trace element metabolism, e.g. Wilson disease
  - Others, e.g. α-1 antitrypsin deficiency

When to Suspect an IEM

Clinical spectrum of IEMs is extremely wide, depending on the type and severity of specific enzyme defect and ranges from completely asymptomatic patients to severe and lethal disease in neonatal period. Generally, these babies are normal at birth as toxic metabolites are cleared by placenta.

IEMs, which manifest in neonatal period, are usually severe and frequently lethal. High index of suspicion is essential for early diagnosis of these defects as presentations are usually non-specific and easily confused with more common problems, e.g. infections, hypoxia, etc. Important clinical indicators of IEM are given in **Table 11.11**.

History of consanguinity in parents or similar illness in previous sibling with/without death is an important warning for IEMs in newborns or early infancy. However, most of the fatal IEMs are autosomal recessive and similar family history may not be obvious.

IEMs, which manifest after neonatal period, are usually milder variants of autosomal recessive defects or transmitted by dominant inheritance. Family history of similar or unexplained illness is often present in these cases.

Laboratory Diagnosis in IEM

Precise diagnosis is essential for appropriate genetic counseling. However, considering the costs involved, a step-wise approach is advised in laboratory workup of these cases involving certain baseline investigations before specific tests. In illnesses with intermittent presentation, all biochemical investigations should be done during the symptomatic phase, as these tests may be false-negative during normal phase. Important investigations in IEMs include:

a. ***Baseline investigations*** in all cases:
   - *Blood:* Complete hemogram, sugar, ammonia, electrolytes, liver enzymes, bicarbonates, lactate and pyruvate levels and arterial blood gases.
   - *Urine:* Color, odor, pH, reducing sugar, ketones, ferric chloride test.
   - *Others:* CSF, nerve conduction studies, etc.

b. ***Specific investigations*** for suspected cause:
   - *Biochemical* estimations of metabolic substrates, e.g. phenylalanine.
   - *Tissue biopsies*, e.g. liver, muscle, bone marrow or skin biopsy for storage disorders.
   - *Specific enzyme assays* in blood or other tissues.

c. ***Molecular diagnosis*** for exact genetic defect in the index case and suspected carriers, as discussed in previous chapter using amplification, e.g. PCR or sequencing tests, e.g. NGS (Ch 11.4).

d. ***Prenatal diagnosis*** by enzyme studies or molecular tests in chorionic villous biopsy or cultured amniotic cells (Ch 11.5).

In morbidly sick children with suspected IEM, it is advised to collect following samples for later studies and genetic counseling: (a) clinical photograph, (b) relevant X-rays, (c) 5–10 ml of blood in heparin and EDTA vials, (d) urine sample, (e) CSF sample, (f) skin, liver, muscle and bone marrow biopsy. All these samples should be adequately stored and transported for further studies.

Some important IEMs from the Indian perspective, are discussed here in greater details.

11.6.1 DISORDERS OF AMINO ACID METABOLISM

Proteins are complex organic nitrogenous compounds made up of smaller units-*amino acids,* which are part of almost all enzymes required for human metabolism. Common IEMs of amino acid metabolism are as follows:

Phenylketonuria: Phenylalanine is an essential amino acid, which is degraded into tyrosine, if not utilized. PKU is the commonest IEM, due to deficiency of enzyme *phenylalanine hydroxylase* (*classical PKU*) or its cofactor *tetrahydrobiopterin* (*malignant PKU*), essential for this degradation. Consequently, un-degraded phenylalanine accumulates in blood and tissues or gets converted into phenylpyruvic acid or phenylethylamine by alternate pathways, which are excreted in urine. Excess phenylalanine prevents utilization of other amino acids by developing brain, leading to progressive neurological damage.

Clinically, children with *classic PKU*, which accounts for >98% cases, are normal at birth and usually manifest at 2–3 months with—(a) progressive mental retardation, (b) neurological features, e.g. irritability, seizures and hypertonia (c) fair complexion with blond hair, blue eyes and occasionally eczema due to tyrosine deficiency, which is essential for melanin production, and (d) mousy odor in urine due to excretion of alternate phenylalanine products.

Diagnosis depends on—(a) plasma phenylalanine levels >2 mg/dl, with (b) altered plasma phenylalanine: tyrosine ratio (>1:3). Urinary excretion of alternate metabolites may be used for screening as *Guthrie test* or *Ferric chloride test* (Add few drops of 1% ferric chloride to fresh urine, which turns deep green due to presence of phenylpyruvic acid). Molecular diagnosis is confirmatory.

Neonatal screening for PKU is widely practiced in many countries, involves whole-blood phenylalanine assay after 48–72 hours of birth by a semi-quantitative bacterial inhibition assay on dried blood spot. Diagnosis should be confirmed by quantitative plasma chromatography as transient hyperalaninemia is not uncommon in newborns.

Treatment aims to reduce phenylalanine/metabolites levels to minimize brain damage. Controlled dietary restriction of phenylalanine using commercial formula, is the key of successful management, which should begin within 1–2 weeks of life and continued till at least 8–10 years.

During dietary restriction, plasma phenylalanine levels should be closely monitored to maintain between 3–15 mg/dl, as over-restriction may lead to deficiency. Adequate dietary intake of tyrosine is essential as its endogenous synthesis is impaired in PKU.

Pregnant mothers with untreated PKU are at risk for (a) spontaneous abortions, (b) babies with mental retardation, microcephaly, agenesis of corpus callosum and heart defects. Prospective mothers should begin low phenylalanine diet before conception to maintain plasma phenylalanine levels <10 mg/dl.

Malignant PKU, carries poor prognosis with rapid neurological deterioration within few months of life. Apart from dietary phenylalanine restriction, some cases may benefit with co-factor BH4 supplementation and/or therapy with neurotransmitter precursors, e.g. L-dopa or 5-HT, to prevent neurological damage.

Tyrosinemia: Tyrosine is a precursor of many important human proteins, e.g. dopamine, norepinephrine, epinephrine, melanin and thyroxine. *Hypertyrosinemia* is seen in many inherited enzyme defects or acquired disorders, e.g. liver failure, scurvy and hypothyroidism.

Clinically, Hereditary tyrosinemia (Tyrosinemia type I) is an autosomal recessive deficiency of *Fumarylacetoacetate hydrolase enzyme*, which presents with:

- Failure to thrive and developmental retardation,
- *Acute hepatic crisis* with fever, vomiting, jaundice, hypoglycemia, hemorrhagic tendencies and a *cabbage like odor* due to accumulated methionine metabolites. Crises are often precipitated by intercurrent infections and resolve spontaneously or progress to cirrhosis or hepatic carcinoma in survivors.

- *Episodic acute peripheral neuropathy*, also triggered by intercurrent infections, presents with severe leg pain, hypertonia and motor weakness. These episodes may recover within a week or terminate into respiratory failure and death.
- *Fanconi-like syndrome* due to renal tubular dysfunction with metabolic acidosis, hyperphosphaturia with nephrocalcinosis and hypophosphatemia with vitamin D resistant rickets.

Early onset cases usually die by 2 years, while others may survive till 8–10 years before death due to cirrhosis or hepatic tumors.

Diagnosis must be suspected on presence of succinylacetoacetate and succinylacetone in serum and urine, confirmed by molecular test by sanger or next generation sequencing. *Prenatal diagnosis* by NGS or enzyme assay in chorionic villous biopsy or succinylacetone levels in amniotic fluid is possible.

Treatment includes dietary restriction of tyrosine and phenylalanine to retard progression of disease, though liver transplant as early as possible is the only effective therapy. An alternate enzyme inhibitor Nitisinone or NTBC (PO 1 mg/day), an inhibitor of the upstream enzyme 4-HPP,) is the mainstay of treatment to prevents toxic metabolite formation. However, as it does not restrict tyrosine formation, diet restriction is mandatory. Liver transplant is recommended only in case of acute liver failure and hepatocellular carcinoma.

Tyrosinemia type II (oculocutaneous tyrosinemia) presents with mental retardation, self-mutilating behavior and herpetiform corneal ulcers in *infancy* due to tyrosine deposition; and palmar/planter punctuate hyperkeratosis in *older children*, which responds well to dietary restriction.

Transient tyrosinemia of newborn is usually seen in preterms on high-protein diet, due to delayed maturation of enzyme *4-hydroxy phenylpyruvate dioxygenase.* Most cases are asymptomatic but some may develop lethargy, poor feeding, decreased motor activity due to high phenylalanine levels. While most cases recver spontaneously in 3–4 weeks, symptomatic cases need dietary protein restriction and vitamin C supplementation (200–400 mg/d).

Albinism denotes a group of genetic disorders with defective biosynthesis and distribution of melanin due to enzyme *tyrosinase* deficiency, despite normal number of melanocytes. Melanin is mainly synthesized in skin, hair follicles and eye (choroids/iris), from tyrosine by a melanocyte organelle—*melanosomes*.

Clinically, Albinism may be *generalized* or *localized*, though all variants have some degree of hypopigmentation of hair and skin, with/without eye involvement. Hypopigmented skin tends to burn on exposure to sunlight, hair are white and silky and those with ocular involvement have translucent/pinkish or bluish sclera with photophobia, diminished visual acuity and strabismus. Blindness and skin cancers are common in severe albinism.

Management depends on severity and includes: (a) avoidance of sun exposure and use of sun-protection creams, (b) ophthalmic support with anti-glare lenses, (c) vocational support, and (d) genetic counseling.

Important variants of albinism include:

- ***Oculocutaneous albinism type I*** (OCA-1), is the most severe form with complete lack of pigment in skin/hair and eyes since birth, though some pigmentation may occur with advancing age.
- ***Oculocutaneous albinism type II*** (OCA-2), the commonest type with partial tyrosinase activity, presents at birth with some pigmentation of skin/eyes and yellowish hair and continue to collect pigment throughout the life.
- ***Ocular albinism*** is limited to eyes with near-normal skin/hair pigmentation and hair bulb tyrosinase activity. Most cases are X-linked.
- ***Partial albinism*** may also be associated with immunodeficiency states, e.g. *Chédiak-Higashi syndrome* (with neutropenia and increased susceptibility to infection), and *Hermansky-Pudlak syndrome* (with platelet dysfunction and bleeding tendencies).
- ***Localized albinism***, limited to a small part of skin/hair, is usually auotosomal dominant and may be present at birth or develop over time. Two important syndromes associated with localized albinism are – *Piebaldism* with white forelock at birth with/out white macules over face, trunk and limbs; and *Waardenburg syndrome* with white forelock, heterochromia iridis and sensorineural deafness.

Homocystinuria, an autosomal recessive disorder of methionine metabolism, is the second commonest error of amino acid metabolism. **Classic homocystinuria**, the commonest variant, denotes deficiency of enzyme *cystathionine β-synthetase*, which leads to accumulation of homocystine (an intermediate metabolite) and methionine (dietary amino acid) in various body fluids and tissues.

Clinically, these cases are asymptomatic in infancy and usually manifest at 3–4 years of age with:

- *Ocular complications*, e.g. ectopia lentis with consequent myopia, iridodonesis, glaucoma, cataracts and retinal detachment/optic atrophy;
- *Skeletal manifestations* with generalized osteoporosis and marfanoid features, e.g. tall and thin stature, arachnodactyly, scoliosis, pectus excavatum, genu valgum, etc.;
- *Neurological manifestations*, e.g. mental retardation and psychiatric/behavioral disorders; and
- *Susceptibility to thromboembolic episodes*, e.g. cerebrovascular strokes, renovascular hypertension, pulmonary embolism, etc.

Diagnosis rests on elevated levels of homocystine (>100 µmol/L) and methionine (>50 µmol/L) in plasma as well as in urine. It is confirmed by enzyme assay or molecular testing in liver biopsy specimen. *Cyanide nitroprusside test* is a simple screening test in these cases to detect presence of homocystine in urine.

Prenatal diagnosis is possible by enzyme assay in cultured amniotic cells or chorionic villi. Whole blood methionine estimation is used for *neonatal screening*.

Treatment with high doses of Pyridoxine (200–1000 mg/d) is effective in ~40% cases and should be continued throughout the life, along with dietary methionine restriction and cysteine, folate and B_{12} supplementation

Non-responsive cases may benefit with betaine therapy (trimethylglycine 100 mg/kg/day q12hr), which stimulates reconversion of homocystine into methionine.

Hartnup disease, an autosomal recessive disorder with mutation in *SLC6A19* gene causing *defective transport of various neutral amino acids*, specially tryptophan, across the gut mucosa and renal tubules is not uncommon but usually asymptomatic. Clinical manifestations are usually attributable to: (a) nicotinamide deficiency—an end-product of tryptophan metabolism, and (b) accumulation and bacterial decomposition of unabsorbed amino acids in gut, which are then absorbed and excreted in urine as indole derivatives.

Clinically, these cases present with:

- *Cutaneous photosensitivity* with pellagra-like rash or chronic eczema, and
- Intermittent episodes of cerebellar ataxia and psychiatric disturbances.

Symptoms are usually exacerbated after diarrhea or low-protein diet. Long, spontaneous remissions are common.

Diagnosis rests on: (a) selective aminoaciduria with normal excretion of non-neutral amino acids, e.g. arginine, proline or hydroxyproline, and (b) heavy urinary excretion of indole derivatives, e.g. indican. Indicanuria, on oxidation into indigo-blue after air exposure, leads to *blue staining of diapers**. Plasma levels of tryptophan and other neutral amino acids are usually normal due to alternative modes of absorption.

**Blue-diaper syndrome is a familial disorder with indicanuria, hypercalcemia and nephrocalcinosis.*

Treatment includes high protein diet to replenish urinary loss of amino acids along with nicotinamide supplements (50–300 mg/day) in symptomatic cases and avoidance of sun-exposure.

Alkaptonuria, the *first identified IEM*, is a rare autosomal recessive disorder with deficiency of *homogentisic acid oxidase* enzyme, essential for degradation of *homogentisic acid*-an intermediate metabolite of tyrosine metabolism. Consequent accumulation of homogentisic acid in tissues leads to black pigmentation and destruction of connective tissues (*ochronosis*) and increased excretion in urine, which turns black on oxidation.

Clinically, these cases are essentially asymptomatic in childhood except black discoloration of urine on standing, specially if it is alkaline.

Most cases manifest in adults with: (a) *ochronosis*, i.e. black pigmentation of sclera and ear/nose cartilage, (b) progressively degenerative arthritis, specially involving spine and large joints. Nephrolithiasis due to renal pigment deposits may develop in later stages.

Diagnosis is based on elevated levels of homogentisic acid in urine and bi-allelic pathogenic variant in *HGD* gene. Homogentisic acid is a strong antioxidant and its presence in urine is indicated by *black reaction with Benedict* or *Fehling agent*. (d/d black urine include phenol poisoning and melanotic tumors)

Treatment is non-specific, though vitamin C therapy (PO 1 gm/d) and Nitisinone (PO 1 mg/day) may delay ochronosis and degenerative arthritic changes. NTBC has shown to slow progression of disease and is approved for treatment in some European countries. Physiotherapy is recommended to promote strength and flexibility.

Organic acidemia or aciduria, is a group of amino-acidopathies due to enzymatic defects in catabolism of *three* essential branched-chain amino acids, i.e. *valine, leucine* and *isoleucine*. Most of these disorders present in neonatal period with persistent metabolic acidosis and neurological dysfunction, with/without hyperammonemia.

Organic acidosis with wide anion gap (>15 mEq/L) is the hallmark of these disorders, though many other inborn errors with metabolic acidosis **(Table 11.16)** must be excluded in differential diagnosis.

Maple syrup urine disease (MSUD) is a rare autosomal recessive defect in decarboxylation of these branched chain amino acids due to deficiency of a complex enzyme system—*branched-chain-ketoacid dehydrogenase*. Consequent accumulation of intermediate metabolites in body fluids and their excretion in urine leads to metabolic acidosis, neurological manifestations and a typical *maple syrup-like odor in urine.*

TABLE 11.16: IEMs with metabolic acidosis

a. Carbohydrate defects (Hyperketotic acidosis)
- Disorders of gluconeogenesis, e.g. GSD
- Disorders of pyruvate metabolism
- Ketotic hypoglycemia

b. Fatty-acid oxidation defects (Hypoketotic acidosis)
- Medium chain aceyl CoA dehyrogenase deficiency
- Carnitine deficiency
- Biotinidase deficiency

c. Amino acid defects (Organic acidemia)
- Branched-chain organic acidurias
- *Others:* Hyperlysinemia

Clinically, classic MSUD manifests within first week of life with poor feeding, vomiting and tachypnea; and rapidly progress to develop neurological features, i.e. coma, seizures and alternate periods of hypotonia and hypertonia (*extensor spasms*). Most cases die in infancy due to severe ketoacidosis and cerebral edema, while mental retardation and neurological deficit is common among survivors.

Other variants present with intermittent ketoacidosis and neurological manifestations during stress, e.g. infections; or a mild late-onset disease beyond infancy with mental retardation, seizures and typical urinary odor.

Diagnosis must be suspected in a case with typical urinary odor, metabolic acidosis, hypoglycemia and ketonuria with *navy blue color on ferric chloride test*. A useful screening test is the development of yellowish precipitate on addition of dinitrophenylhydrazine in urine. Confirmation requires NGS and aminoacidogram to show marked elevation of branched amino acids.

Treatment includes: (a) life-long dietary restriction of branched-chain amino acids, especially leucine by using BCAA free formula. Supplementation with isoleucine and valine may be required; (b) exchange transfusion or hemodialysis to eliminate accumulated organic acids in acute phase, and (c) prevention of catabolic states, i.e. infections, which may precipitate the crisis. Thiamine supplementation may be beneficial in some mild cases. Liver transplantation is the definitive treatment.

Disorders of branched chain amino acids, other than MSUD, e.g. *Methylmalonic aciduria (MMA)*, *Isovaleric academia (IVA)*, and *Propionic aciduria* (PA) present with similar manifestations, i.e. metabolic ketoacidosis and neurological manifestations in early infancy and need to be differentiated on plasma aminoacidgram and Gas Chromatography Mass Spectrometry (GCMS) *urine in isovaleric acidemia has typical 'sweaty feet' odor.*

Management includes supplemental vitamin B_{12} to those MMA cases who are known to be vitamin B_{12} responsive; restricting natural protein, particularly of propiogenic amino acid precursors, while maintaining a high-calorie diet. Carnitine supplementation is required to improve the excretion of propionic acid in PA. Metronidazole is given to reduce the propionate producing gut bacteria. Liver transplant is the definitive management.

Urea cycle defects (hyperammonemia): Ammonia, a highly neurotoxic substance, is regularly produced on catabolism of various amino acids and rapidly degraded in liver by *Krebs-Henseleit* cycle to urea for excretion.

Hyperammonemia is seen in many *inherited defects*, e.g. (a) urea cycle defects and (b) organic acidemias, etc.; or *acquired hepato-cellular disorders*, e.g. (c) acute hepatic failure, (d) Reye syndrome, and (e) portal vein obstruction.

Urea cycle defects include inherited deficiency in one of the five major Krebs-cycle enzymes, namely *carbamyl phosphate synthetase* (CPS), *ornithine transcarbamylase* (OTC), *argininosuccinate synthetase* (AS), *argininosuccinate lyase* (AL) and *arginase*; leading to hyperammonemia and neurological features. All of them are autosomal recessive except OTC deficiency, which is commonest among all urea-cycle defects and inherited as X-linked dominant.

Clinical manifestations of urea cycle defects vary according to the type and severity of enzyme defects, broadly divided into:

a. *Severe neonatal hyperammonemia* (>1000 µmol/L) due to complete urea-cycle enzyme defects, presents within few hours/days of birth with poor feeding, vomiting, hypotonia and tachypnea; rapidly progressing to coma, intractable seizures and death, if untreated.
b. *Moderate neonatal hyperammonemia* (200–400 µmol/L) due to partial urea-cycle enzyme defects or organic acidemias, presents in newborns with mild features, e.g. unexplained lethargy and poor feeding.
c. *Late-onset hyperammonemia* is asymptomatic till the baby is on low-protein breast milk, only to manifest after introduction of high-protein weaning foods or infections. These cases present with intermittent episodes of vomiting, lethargy, seizures and coma, often misdiagnosed as recurrent Reye syndrome. Plasma ammonia levels are high (200–500 µmol/L), but only during episodes.
d. *Transient neonatal hyperammonemia*, an unexplained hyperammonemic state is usually seen in preterms, which is either asymptomatic or manifests soon after birth with features mentioned in 'a' above. Most cases recover spontaneously after 6–8 weeks, unless die during acute crisis.

Diagnosis depends on high index of suspicion (often misdiagnosed as neonatal septicemia) and presence of hyperammonemia >200 µmol/L. Identification of specific urea-cycle enzyme defects depends on amino acid profile in plasma or urine.

Treatment of acute hyperammonemic states include:

- Complete elimination of proteins in diet, except an IV mixture of essential amino acids as 0.25 gm/kg/day;
- Adequate provision of calories as IV dextrose and lipids, to prevent endogenous protein breakdown;
- Gut sterilization with lactulose therapy to reduce intestinal ammonia production by bacterial activity;
- Urinary elimination of ammonia in excretable conjugate forms with sodium benzoate and arginine (PO 250–500 mg/kg/day). Arginine is not used in arginase deficiency.
- Hemodialysis or hemofiltration in severe cases.

On recovery, these cases should continue on low protein diet (<1 gm/kg/d) and chemical conjugates, e.g. sodium benzoate, sodium phenylacetate etc (orally, in abovementioned doses), along with avoidance of catabolic states, e.g. infections and heavy meals.

11.6.2 DISORDERS OF LIPID METABOLISM

Disorders of fat metabolism may be broadly divided into five categories: (a) mitochondrial fatty acid oxidation defects, (b) peroxisomal disorders, (c) lipoprotein disorders, (d) lipid storage disorders or lipidoses, and (e) mucolipidoses.

A. Mitochondrial Fatty Acid Oxidation Defects

Mitochondrial oxidation of fatty acids is an essential energy-producing pathway, specially during starvation and exercise. In skeletal and cardiac muscles, fatty acids are completely oxidized into CO_2 and water. In liver, ketones (acetoacetate and β-hydroxybutyrate) are end-products of fatty acid oxidation, which serves as fuel for peripheral tissues, e.g. brain.

Many genetic defects of mitochondrial fatty acid oxidation, all autosomal recessive, are known. Almost all are characterized by acute hypoglycemic coma on starvation with/without other features, e.g. cardiomyopathy, muscular weakness or rhabdomyolysis. As these cases manifest only on fasting, they are usually misdiagnosed as Reye syndrome or sudden infant death syndrome. *Absence of urinary ketones despite hypoglycaemia is a diagnostic clue in these cases.*

Medium chain acyl-CoA dehydrogenase deficiency is the commonest fatty acid oxidation defect, presenting between 6 months and 3 years of life, with acute episodes of vomiting, coma, seizures, hepatomegaly and, hypoketotic hypoglycemia after prolonged fasting (12–16 hours).

Acute episodes should be rapidly treated with IV dextrose to prevent lipolysis, while further attacks can be prevented by avoiding prolonged starvation, use of corn starch 2gm/kg/day, medium chain triglyceride (MCT) oil, and overall low fat diet. Attacks become less frequent with advancing age. Cardiomyopathy and muscle weakness is absent.

Carnitine deficiency: Carnintine is a critical cofactor in transport of fatty acids across the mitochondrial membrane, specially in heart and muscles. It is synthesized from lysine in humans as well as also present in red meat and dairy products. Carnitine deficiency is either *primary* (dietary) or *secondary* due to increased excretion in fatty acid oxidation defects.

Clinically, these cases may present with *fasting hypoketotic hypoglycemia* in infancy and early childhood, though most common presentation is cardiomyopathy and generalized muscle weakness at 2–4 years of age. Some cases may present with acute rhabdomyolysis, myoglobinuria and renal failure. Low plasma carnitine levels are diagnostic and treatment includes oral carnitine supplements (50–100 mg/kg/d q8hr).

Biotinidase deficiency: Biotin is an essential cofactor for many carobxylase enzymes involved in organic acid metabolism. Biotinidase enzyme frees the biotin from carboxylase enzymes for re-use, after metabolic reaction. Inherited biotinidase deficiency limits re-use of biotin and increases its dietary requirement, not fulfilled by intake.

Clinically, these cases present in neonatal period or infancy with: (a) *neurological manifestations*, e.g. seizures and hypotonia, (b) *skin manifestations*, e.g. alopecia and skin rash, (c) *metabolic acidosis* due to excessive urinary excretion of unmetabolised organic acids, and (d) *immunodeficiency* states. Megavitamin therapy with high doses of biotin (10–40 mg/d) is highly effective.

B. Peroxisomal Disorders

Peroxisomes are subcellular organelles, present in all cells except mature erythrocytes, where very-long-chain fatty acids are oxidized. Peroxisomal disorders include a genetically heterogeneous disorders due to-either defective formation of peroxisomes (multiple enzyme defects) or defective function of one of enzymes located within them (single enzyme defects).

Peroxisome biogenesis disorder is a collective term for three overlapping clinical syndromes due to defective peroxisome formation—*Zellweger syndrome, neonatal adrenoleukodystrophy and infantile Refsum disease*, in order of decreasing severity.

- *Zellweger syndrome* is usually fatal in infancy and presents with—(a) mongoloid facial features, (b) generalized hypotonia, (c) neonatal seizures, and (d) ocular abnormalities.
- *Neonatal adrenoleukodystrophy* usually presents in late infancy with developmental regression, seizures, and visual/hearing impairment.
- *Infantile Refsum disease* presents in early childhood with ataxic gait, mental retardation, sensorineural deafness, pigmentary retinal degeneration and facial dysmorphism.

Diagnosis of these disorders is mainly clinical, supported by plasma assays for very-long-fatty acids.

Treatment is largely supportive including physical and occupational therapy, hearing aids, etc.

C. Lipoprotein Disorders

Lipoprotein disorders are more important in adults due to association with atherosclerosis and consequent morbidity. Abetalipoproteinemia is the most important lipoprotein disorder in children.

Abetalipoproteinemia is rare inherited disorder of fat malabsorption, due to autosomal recessive deficiency of β-lipoproteins, essential for chylomicron formation.

Clinically, it is characterized by: (a) failure to thrive, (b) steatorrhea, (c) neurological manifestations due to vitamin E deficiency and spinocerebellar degeneration, e.g. ataxia, spastic gait, loss of position/vibration

senses and absent deep tendon reflexes, and (d) ocular manifestations, e.g. atypical retinitis pigmentosa. While malabsorption presents since early childhood, neurological and retinal changes appear beyond first decade of life.

Diagnosis rests on: (a) presence of *acanthocytes* in peripheral smear and (b) extremely low cholesterol (<50 mg/dl), LDL and VLDL levels.

Treatment is non-specific, including supplementation of fat-soluble vitamins and dietary restriction of long chain fats.

D. Lipid Storage Disorders (Lipidoses)

Glycosphingolipids are essential components of cell membranes which are regularly degraded in lysosomes by lysosomal enzymes. Genetic errors in the formation of lysosomes or its hydrolytic enzymes, transport of degradation material in/out of the lysosomes or excessive destruction of lysosomal enzymes, present with diverse disorders. *Common lysosomal disorders include—lipid storage disorders, mucopolysaccharidosis and glycoproteinosis.*

Lipid storage disorders denote a heterogeneous group of genetically inherited defects in activity of these enzymes, leading abnormal intra-lysosomal accumulation of related lipids and variable clinical presentations. Storage within the neuronal cells present with neurodegenerative disorders (Ch 18.15) while visceral storage can lead to organomegaly, skeletal deformities and other manifestations.

All lipid storage disorders are autosomal recessive, except Fabry disease, which is X-linked recessive. Some important lipidoses are as follows:

Gaucher disease (GD) is the commonest lysosomal storage disorder and lipidosis, most prevalent in Ashkenazi Jews. It is a multisystem disease, due to deficiency of a lysosomal enzyme *glucocerebrosidase*, leading to intracellular accumulation of undegraded glycolipid *glucosylceramide* in reticuloendothelial system.

Clinically, Three variants are known:

- *Type I (adult non-neuropathic form*), accounts for 99% cases and presents at any age beyond early childhood with: (a) *progressive massive splenomegaly* with/without hepatomegaly and signs of hypersplenism, (b) *skeletal involvement* with bone pains and pathological fractures in ~ 20–50%, due to bone marrow expansion from foamy lipid-filled cells. Neurological manifestations are absent.
- *Type II (acute neuropathic)* presents in infancy with: (a) rapidly progressive neurodegenerative course with severe developmental retardation and hypertonia, (b) failure to thrive, and (c) extensive visceral involvement with organomegaly. Most patients die by 2 years due to respiratory complications.
- *Type III (chronic neuronopathic)* with intermediate course, presents at 1–3 years of age with slow progression of neurological and visceral involvement These cases may survive till 10–15 years.

Diagnosis: Presence of *Gaucher cells*, i.e. large foamy PAS +ve cells with characteristic *wrinkled paper appearance* due to intracytoplasmic inclusions, in reticuloendothelial system, e.g. bone marrow/splenic puncture *or* liver biopsy is a pathological hallmark of Gaucher disease. However, Gaucher cells may also be seen in myeloma and graulocytic leukemia.

In this era of advanced diagnostic techniques, invasive tests are avoided and diagnosis is confirmed by enzyme assay *glucocerbrosidase* in leukocytes or skin fibroblasts, which also helps in carrier detection. *Prenatal diagnosis* by enzyme assay or DNA analysis in aminocytes/chorionic villous cells is possible, though targeted variant testing is preferred for accuracy.

Treatment is largely symptomatic with splenectomy and blood transfusions, if necessary. Bone marrow transplant is curative but with high morbidity and mortality.

- ***Enzyme replacement therapy*** with recombinant β-*glucocerebrosidase* (imiglucerase, velaglucerase or Taliglucerase) is the standard of care for Gaucher type I and III, given life-long IV 30–60 IU/kg alternate week. It is not recommended in type II as it does not cross the blood brain barrier.
- ***Substrate reduction therapy*** with oral Eliglustat or Miglstat to reduce production of fatty material may be useful in mild adult cases, if ERT is not possible.

Splenectomy is to be avoided except in extreme circumstances like splenic rupture. Supportive care like blood transfusions will be required. Bone marrow transplant has high morbidity and mortality.

Niemann-Pick disease a rare lipidosis with six known subtypes, of which two (type A and B) are most important in children, both due to deficiency of enzyme *sphingomyelinase* and consequent intralysosomal accumulation of sphingomyelin and other lipids.

- ***Type A*** presents at ~6 months of age with: (a) failure to thrive, (b) hepatosplenomegaly with lymphadenopathy, and (c) progressive neurodegeneration, i.e. spasticity and development delay.
- ***Type B*** presents beyond infancy with progressive hepatosplenomegaly and pulmonary involvement with diffuse nodular infiltrations on X-ray. Neurological manifestations are absent with normal intelligence. Severely affected children may develop significant pulmonary compromise or cirrhosis.

Diagnosis rests on presence of characteristic foamy *Niemann-pick cells* in bone marrow, confirmed by acid sphingomyelinase enzyme assay in leukocytes or cultured fibroblasts. *Prenatal diagnosis* is possible but carrier detection is unreliable on enzyme studies and

needs genetic workup. Cherry red spot is seen on fundus examination.

Treatment is largely supportive and non-specific. ERT is not yet available though Miglustat is approved for substrate reduction in some countries. Enzyme replacement therapy (Olipudase alfa) is available for type B or type A/B disease.

Gangliosidoses is a group of autosomal recessive disorders of *ganglioside* (a normal lipid in cell membrane) catabolism due to various enzyme defects, leading to its excess accumulation within the neuronal cells. These defects are broadly classified into two major groups—GM_1 *gangliosidoses* (β-galactosidase-1 deficiency) GM_2 *gangliosidoses* (Hexosaminidase deficiency); both presenting as neurodegenerative illnesses with variable age and severity of presentation (Ch 18.15).

Metachromatic leukodystrophy (MLD) due to *Arylsulfatase-A deficiency* and consequent accumulation of *cerebroside sulfate* within the myelin sheaths is the commonest neurodegenerative disorder in India (Ch 18.15).

Krabbe disease due to *Galactocerebrosidase* deficiency with accumulation of *galactosylceramide*, is a rare but fatal disorder, presenting in infancy as neurodegenerative disease with optic atrophy, and death by 2–3 years.

Fabry disease (*α-galactosidase deficiency*) is the only X-linked recessive lipidoses, presenting in late childhood with: (a) multiple angiokeratomas with hypohidrosis and corneal/lenticular opacities, (b) acroparesthesias, i.e. *fabry crises* with episodes of severe burning pain in hands/feet, and (c) vascular disorders of kidney (proteinuria, azotemia), heart (myocardial ischemia, hypertension) and brain (strokes).

Enzyme replacement therapy (IV Agalsidase beta or alfa) is available.

Farber disease (*ceramidase deficiency*) begins by the end of infancy with painful joint swellings and nodule formation, followed by failure to thrive, hoarseness due to vocal nodules, and moderate neurodegeneration in some cases. Most of them die in second decade of life.

Wolman disease (*acid lipase deficiency*) presents in first week of life with failure to thrive, vomiting, steatorrhea, hepatosplenomegaly and hyperlipidemia. Adrenal calcification is pathognomonic. Most cases die by 6 months. Enzyme replacement therapy with sebelipase alfa has been recently approved for this disorder. Otherwise bone marrow transplant was the conventional mode of therapy.

E. Mucolipidoses

Mucolipidoses is a group of two rare autosomal recessive disorders with defective transport of lysosomal enzymes and consequent cellular deficiency of all lysosomal enzymes—**I-cell disease** and **pseudo-Hurler polydystrophy**. Clinical manifestation of both resemble Hurler syndrome (MPS-I), except absence of mucopolysaccharoiduria.

11.6.3 DISORDERS OF CARBOHYDRATE METABOLISM

Dietary glucose, consumed as *disaccharides*, i.e. sucrose, lactose and maltose or *polysaccharides*, e.g. starch, is the principle substrate for energy (ATP) generation via the processes of *glycolysis* (glucose > pyruvate) or *mitochondrial oxidation* (pyruvate > CO_2 and water). Unutilized glucose is stored as *glycogen* in liver and muscles, which may be reconverted into glucose *by glycogenolysis* during high requirements, e.g. exercise. Thus, maintenance of euglycemic state is principally a function of balance between free glucose and stored glycogen. Galactose and Fructose, other energy-producing monosaccharides, are of limited significance. Galactose, derived from milk products as *Lactase* (glucose + galactose), is an important component of many glycolipids, glycoproteins and glycosaminoglycans. *Neoglucogenesis*, i.e. *de novo* glucose synthesis from other sources, e.g. fats, also contribute to euglycemic state.

Disorders of carbohydrate metabolism may be broadly divided into: (a) defects in glycogen degradation, i.e. glycogen storage disorders, (b) disorders of galactose or fructose metabolism, e.g. galactosemia, (c) disorders of glucose utilization, e.g. pyruvate metabolic defects, mitochondrial oxidation defects, etc., and (d) disorders of neoglucogenesis. The last two groups predominantly presents with lactic acidosis.

Glycogen storage disorders (GSD) include heterogeneous group of inborn errors in carbohydrate metabolism, all characterized by *abnormal accumulation of normal or altered glycogen* in various tissues, due to various enzymatic defects in synthesis or degradation of glycogen.

More than 14 forms of GSDs are known so far, classified numerically in order of identification *or* the principle organs of involvement, e.g. liver (Ia, Ib, III, VI, VI, VII, IX, XI, 0), muscles (V, VII), or both (II, III). All GSDs are autosomal recessive, except IXb, which is X-linked recessive. Some important forms are as follows:

Type I (von Gierke disease) is the commonest GSD with two variants (a and b) which usually present in early infancy with: (a) gross hepatomegaly and renal enlargement, (b) doll-like facies with short stature, (c) normal mental development, and (d) recurrent hypoglycemia or lactic acidosis, specially on fasting. Bleeding tendencies are common due to platelet function defects. Type Ib variant is also associated with recurrent infections due to neutropenia or neutrophil function defects.

Diagnosis rests on clinical suspicion, abnormal plasma glucose, lactate and lipid values and no rise of glucose

levels after glucagon administration. Diagnosis rests on next generation sequencing. Liver biopsy for enzyme assay is avoided, being an invasive procedure.

Treatment aims to maintain normoglycemia by frequent feedings or continuous gavage and introduction of uncooked corn starch in diet as a source of slow-release glucose (1.5–2.5 gm/kg every 4–6 hours), along with supportive and symptomatic measures. Supporting measures include control of acidosis, infections and bleeding tendencies, allopurinol therapy for hyperuricemia and regular vitamin/mineral supplementation. Untreated cases may die in infancy during hypoglycemia/acidotic episodes, survivors may improve with age, though some develop gout, uric acid nephropathy and hepatic adenomas in adulthood. Patients of GSD1b with neutropenia may require G CSF injections.

Type II (Pompe disease) is a lysosomal disorder with lysosomal storage of glycogen in muscles due to acid alpha-glucosidase deficiency.

Clinically, it presents with two phenotypes of generalized myopathy, with different age of onset and severity:

a. *Infantile form* presents in neonatal period with: (a) generalized hypotonia or '*floppy baby*' with feeding difficulties, and (b) cardiomegaly and CCF due to progressive hypertrophic cardiomyopathy. Most cases die in infancy due to aspiration or respiratory failure.
b. *Juvenile form* presents with delayed motor development or difficult walking in late childhood, followed by gradual progressive proximal muscle weakness, swallowing difficulties and respiratory failure. Most cases die in second decade.
c. *Adult form* is a very slowly progressive proximal myopathy, manifesting beyond 2–3rd decade of life, without cardiac involvement.

Diagnosis is suspected on elevated CPK and LDH levels with EMG showing myopathic features. Muscle biopsy shows presence of glycogen positive vacuoles, though can be avoided by using NGS or demonstration of reduced enzyme activity on DBS. *Prenatal diagnosis* using amniocytes or chorionic villi is possible by targeted variant testing

Treatment includes enzyme replacement therapy (IV Alglucosidase alfa) every 2 weeks, along with supportive cardiac care and physiotherapy.

Other uncommon GSDs include:

- **Type III (Debrancher deficiency)** has two variants—type IIIa, involving liver and muscles both, and type IIIb, with only liver involvement. *Clinically,* it manifests in early childhood with milder features of GSD type I, i.e. hepatomegaly, hypoglycaemic spells and growth failure but *without renal enlargement* (d/d type I). Liver disease tends to improve with age, while muscular weakness and wasting appears and worsens after puberty. Diagnosis rests on next generation sequencing.
- **Type IV (Anderson disease)** presents in infancy with failure to thrive, hepatosplenomegaly and progressive cirrhosis with chronic liver failure and portal hypertension that leads to death by 5 years. Diagnosis rests on next generation sequencing.
- **Type V (McArdle disease)** presents in late childhood/adults with muscle cramps and myoglobinuria after strenuous exercise due to rhabdomyolysis. *Ischemic exercise test*, i.e. no rise in blood lactate but elevated ammonia levels after exercise is a useful screening test for muscle glycogenoses.
- **Type VII (Tarui disease)** has similar presentation as in type V, except—(a) earlier onset with more severe cramps and myoglobinuria, not preventable with high glucose diet, (b) evidence of continued compensated hemolysis with high bilirubin and reticulocyte count,
- **Type VI (Hers disease)** presents with hepatomegaly and growth retardation in early childhood but runs a benign course and improves by puberty without treatment.
- **Type XI (Fanconi-Bickel syndrome)** presents like type IA along with hyperlipidemia, hyperuricemia and renal dysfunction.
- **Phosphoryl kinase deficiency** is clinically heterogeneous group of GSDs, (previously classified as type VIa, VIII-X), where enzyme defects may be limited to liver, muscle or both.

Galactosemia: Galactose, derived from milk and other dairy products, is converted into Glucose-6 phosphate, before utilization as metabolic fuel *or* in synthesis of other galactosides, enzymatic defects in this galactose metabolism lead to excessive accumulation of galactose and its metabolites in various tissues, galactosuria and hypoglycemia, collectively termed as galactosemia. Three major types, all autosomal recessive, are known.

Classical galactosemia denotes deficiency of Galactose-1-phoshate uridyltransferase (GALT) leading to accumulation of Galactose-1 phosphate and its metabolites, toxic to liver and other organs.

Clinically, baby is normal at birth and manifestations begin after 3–4 days of breast feeding with intractable vomiting, diarrhea and failure to thrive. Unconjugated hyperbilirubinemia is common and untreated cases may develop chronic liver disease, cataracts and renal tubular acidosis.

Diagnosis rests on elevated RBC Galactose-1 Phosphate levels (>10 mg/dl) and reduced enzyme activity (<1%) on molecular studies. However, a positive Benedict test in urine but negative urine dipstick test suggesting presence og non-glucose reducing substances is a useful screening test. Universal galactosemia screening in newborns is practiced in many countries.

Treatment involves strict elimination of galactose, i.e. milk/milk products from diet, which may reverse growth failure, cataracts and hepatic dysfunction and prevent further damage. However, mental retardation, if already developed, is irreversible. A soy-based formula may be used for infant feeding

Galactokinase deficiency, a mild variant of galactosemia, is usually asymptomatic except cataracts in older children and biochemical galactosemia/galactosuria. Mental retardation is absent. Diagnosis depends on erythrocyte enzyme assay and rearing on galactose-free diet may prevent/regress cataracts.

Lactic acidosis is a common presentation of many metabolic disorders involving—(a) *glucose utilization*, e.g. pyruvate metabolic defects, mitochondrial respiratory chain defects, etc., and (b) *neoglucogenesis*. While serum pyruvate levels are increased in disorders of neoglucogenesis or pyruvate metabolism, they are normal in mitochondrial oxidation defects.

Lactic acidosis is also seen in many fatty acid oxidation defects (with abnormal serum acylcarnitine profile) and organic acidurias (with presence of unusual organic acids in urine), as well as in acquired states, e.g. hypoxemia.

11.6.4 MUCOPOLYSACCHARIDES

Mucopolysaccharides or *glycosaminoglycans* (GAGs) are major constituents of connective tissue, including chondroitin sulfates, dermatan sulfate, heparan sulfate, keratan sulfate, hyaluronic acid and heparin.

Mucopolysaccharoidoses (MPS) are inherited defects in degradation of these GAGs, due to deficiency of specific lysosomal enzymes, leading to excess accumulation and consequent urinary excretion of various GAGs. Over 10 variants of MPS are known, each with a specific lysosomal enzyme defect, clinical presentation and severity **(Table 11.17)**. All of them are autosomal recessive, except Hunter syndrome, which is X-linked recessive. Some important types of MPS are discussed here:

Hurler syndrome (MPS IH) is the most severe and prototype manifestation of MPS with multiple organ involvement.

Clinically, These babies are normal at birth and usually manifest at 6 months-2 years of age with:

- *Short stature and coarse facial features* with prominent forehead, cloudy cornea, flat-broad nose, thick lips and large tongue **(Fig. 11.10)**;
- *Developmental delay* with poor language development and hearing loss;
- *Hepatosplenomegaly* with protuberant abdomen and frequent umbilical/inguinal hernias;

  Multiple bony deformities (dysostosis multiplex) include large, thick calvarium, dolichocephalic skull with shallow orbits, enlarged and deformed sella turcica, broad-spatulate '*oar shaped*' ribs, anterior hypoplasia (*beaking*) of lumbar vertebrae with kyphosis, short and wide bullet shaped phalanges and deformed pelvis with short femoral head and coxa valga. Long bones have wide diaphyses, irregular metaphyses and poorly developed epiphyses.
- *Others*, e.g. acute cardiomyopathy and communicating hydrocephalus in some cases.

TABLE 11.17: Classification of mucopolysaccharidoses

No.	*G) Name*	*Enzyme def.*	*Stored GAG*	*Face**	*MR*	*HSM*	*CC*	*Bone***
I H	Hurler	α-L-iduronidase	DS, HS	+	+	+	+	+
I S	Scheie	α-L-iduronidase	DS, HS	–	–	–	+	
I H/S	Hurler/Scheie	α-L-iduronidase	DS, HS					
II	Hunter	Iduronate sulfatase	DS, HS	+	+	+	–	+
IIIa	Sanfilippo A	Heparan-N-sulfatase	HS	–	+	–	–	–
	Sanfilippo B	α-N-Acetyl	HS	–	+	–	–	–
		Glucosaminidase						
	Sanfilippo C	Acetyl CoA-α	HS	–	+	–	–	–
		Glucosaminidase						
		acetyltransferase						
	Sanfilippo D	N-acetylgalactosamine	HS	–	+	–	–	–
		-6 sufatase						
IVa	Morquio A	Galactose-6-sulfatase	KS	–	–	–	+	+
	Morquio B	β-galactosidase	KS					
VI	Maroteaux-Lamy	N-acetylgalactosamine-	DS	–	–	–	+	+
		4 sulfatase						
VII	Sly	β-glucuronidase	DS, HS	–	–	+	–	+
IX	–	Hyaluronidase	Hyaluronan	–	–	–	–	–

DS: Dermatan sulphate; **HS:** Heparan sulphate; **KS:** Keratan sulphate; **HSM:** Hepatosplenomegaly; **MR:** Mental retardation; **CC:** Corneal clouding
*Abnormal facial appearance. **Dysostosis multiplex.

Fig. 11.10: Hurler syndrome: (A) Clinical appearance, note corneal clouding (inset); (B) beaking of the vertebrae (arrow).

Most cases develop recurrent respiratory infections, noisy breathing or obstructive airway disease due to facial deformities and die by 10 years.

Diagnosis rests on clinical and radiological findings with urinary excretion of *dermatan and heparin sulfate*. Definitive diagnosis requires molecular testing though specific enzyme assay in serum leukocytes or skin fibroblasts may be used. Prenatal diagnosis is possible using amniocytes or chorionic villous cells.

Treatment is supportive with control of cardio-respiratory complications, orthopedic corrections and hearing support. Although bone marrow transplant in severe phenotypes has shown significant clinical improvement in somatic features, skeletal, ocular and mental abnormalities are irreversible.

Enzyme replacement therapy (IV Laronidase every 2 weeks) reduces the GAG excretion and causes subjective improvement in respiratory symptoms. However, there is not much improvement in skeletal features and cardiac features.

Scheie syndrome (MPS IS) is mildest variant of MPS with onset beyond 5 years of age. These cases have normal stature and intelligence with minimum facial and skeletal features, usually characterized by: (a) joint stiffness, (b) severe corneal clouding, and (c) aortic valve disease.

Hunter syndrome (MPS II) is only X-linked recessive MPS, with two clinical variants—a severe form analogous to Hurler syndrome, and a mild form analogous to Scheie syndrome, except: (a) absence of corneal clouding, and (b) slower progression of somatic and neurological deterioration. Communicating hydrocephalus is common in severe form. Enzyme replacement therapy (IV Idursulfase every week) is available.

Sanfilippo syndrome (MPS III) includes four biochemical diverse but clinically similar types of MPS (A–D), each with different enzyme deficiency. These cases usually present at 2–6 years of age with slowly progressive neurological impairment but only mild somatic disease (coarse hair, hirsutism, mild hepatosplenomegaly and skeletal features). Short stature and corneal clouding is rare. Severe neurological deterioration develops by 6–10 years, with death in adolescence.

Morquio syndrome (MPS IV) is characterized by *normal intelligence but severe skeletal deformities*, i.e. (a) short trunk-short stature due to platyspondyly, i.e. flat vertebrae, (b) short neck with unstable odontoid process, susceptible for atlantoaxial subluxation, (c) kyphoscoliosis with dysplastic hips and flat feet, leading to waddling gait. Joint laxity, mild corneal clouding, hepatomegaly, cardiac valvular lesions and abnormal dentition may be present. Most cases survive till 3–4th decade of life.

Treatment involves enzyme replacement therapy (IV Elosulfase) and supportive care with clinical and neuroimaging monitoring for cervical cord compression and immediate neurosurgical intervention.

Maroteaux-Lamy syndrome (MPS VI), in severe form resembles Hurler syndrome, except absence of developmental delay. However, milder variants may be easily confused with Scheie syndrome. Spinal cord compression due to thickened cervical dura matter is common in mild forms. Enzyme replacement therapy (IV Galsulfase) is available.

Sly syndrome (MPS VII) is the rarest MPS with extremely variable presentation, ranging from hydrop fetalis or severe dysostosis multiplex in newborns, to features resembling Hurler syndrome in older children.

11.6.5 PORPHYRIA

Heme, composed of ferrous iron and protoporphyrins, is an essential constituent of hemoglobin, myoglobin and many other enzymes. The porphyrias are inherited disorders of *heme biosynthesis* due to various enzyme defects **(Fig. 11.11)**, leading to abnormal tissue accumulation and urinary/fecal excretion of porphyrins or their precursors. Cutaneous photosensitivity and neurological involvement are predominant manifestations of porphyrin toxicity, apart from visceral features in some cases.

Porphyrias are classified according to the order of defective enzyme in heme biosynthesis **(Table 11.18)** or the site of expression, i.e. a*cute hepatic porphyrias* (ADP, AIP, HCP, VP) or *erythrocytic porphyrias* (CEP, PCT, HEP, EPP). Of these, most common are acute intermittent porphyria, porphyria cutaneous tarda and erythrocytic porphyria, discussed here in greater details.

Acute intermittent porphyria (AIP), is the commonest genetic porphyria, which usually presents beyond puberty.

Clinically, it present with acute episodes of: (a) severe abdominal pain with/without vomiting, mimicking surgical abdomen, (b) neuropathy with proximal muscle weakness and cranial nerve involvements, and (c) cardiovascular signs, e.g. tachycardia with hypertension,

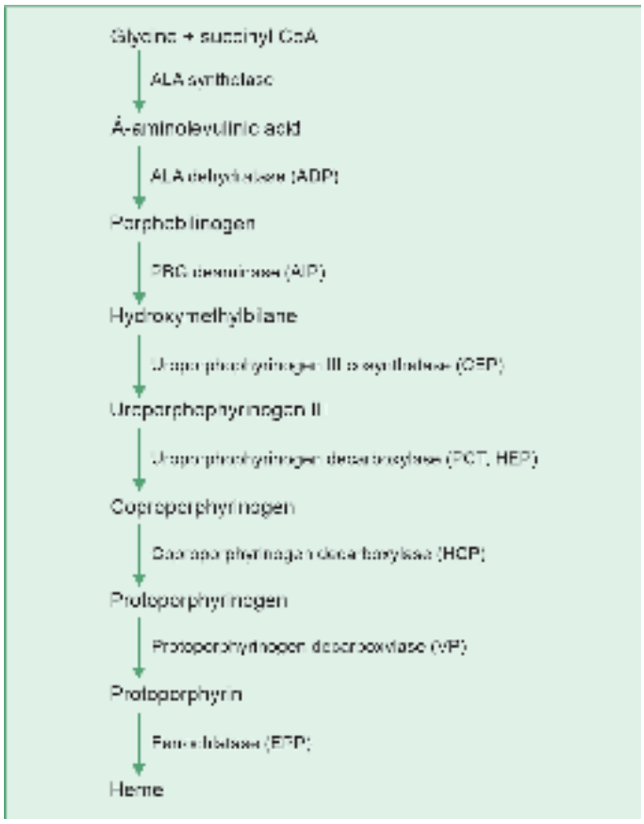

Fig. 11.11: Important steps in heme synthesis and enzymatic origin of various porphyrias.

which may persist even after the episode. Attacks are precipitated by fasting, infections, surgery, drugs/chemical ingestion or hormonal factors, e.g. menses in females. Skin manifestations are absent.

Diagnosis rests on decreased porphobilinogen deaminase activity in erythrocytes, though elevated levels of porphobilinogen in urine on *Watson-Schwartz* screening test or chromatographic studies are highly suggestive.

Treatment is largely supportive during the attack, which may be prevented by adequate caloric intake, avoidance of precipitant drugs and prompt management of infections. IV hematin (4 mg/kg/BD) may curtail severe attacks.

Porphyria cutanea tarda (PCT), the commonest porphyria, which may be inherited (autosomal dominant) or acquired. Acquired PCT is mainly seen in adults after exposure to factors, e.g. alcohol, estrogens or drugs.

Clinically, cutaneous photosensitivity with formation of vesicles over exposed parts of body is pathognomonic of PCT, which may heal with crusting, scarring and residual pigmentation. Neurological or visceral manifestation are absent.

Diagnosis rests on elevated excretion of urinary and fecal porphyrins, specially *isocoproporphyrin* levels in stools. Daily porphyrin excretion in stools exceeds that in urine.

TABLE 11.18: Classification of porphyria

Type	*MOI*	*Skin*	*Neural*	*Visceral*
ALA deficiency porphyria (ADP)	AR	–	+	–
Acute intermittent porphyria (AIP)	AR	–	+	AP
Congenital erythrocytic porphyria (CEP)	AR	+	–	HA
Porphyria cutanea tarda (PCT)	AD	+	–	–
Hepatoerythrocytic porphyria (HEP)	AR	+	–	HA
Hereditary coproporphyria (HCP)	AD	+	+	AP
Varigate porphyria (VP)	AD	+	+	AP
Erythrocytic protoporphyria (EPP)	AD	+	–	–

AP: Abdominal pain, **HA:** Hemolytic anemia, **MOI:** Modes of inheritance

Treatment is symptomatic, though avoidance of sunlight and precipitating factors in acquired disease is necessary.

Erythrocytic protoporphyria (EPP), an autosomal dominant *ferrochelatase deficiency*, typically manifests in childhood, with extreme cutaneous photosensitivity.

Clinically, EPP present with stingy or burning sensations within 1–2 hours of sun exposure followed by erythema and edema. Vesicles are less common but repeated attacks lead to hyperkeratosis of exposed skin and onycholysis. Chronic hepatic disease and gallstones are common. Neuro-visceral involvement is absent.

Diagnosis rests on elevated free protoporphyrin levels in erythrocytes, plasma and stools, with normal urinary porphyrins.

Treatment includes avoidance of sun-exposure and use of topical sunscreen agents to prevent skin burning. Oral administration of β-carotene increases photo-tolerance to some extent.

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CHAPTER

12

Newborn

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Birth is a water-shed event in human life, necessitating various physiological changes to adapt from intrauterine to extrauterine life. Success of this adaptation depends on many biological factors, e.g. genetic composition, gestational age, etc. as well as environmental factors, e.g. maternal health, quality of antenatal and perinatal care and postnatal environment.

12.1 GENERAL TERMINOLOGY

Live birth is defined as *presence of some signs of life after expulsion of baby*, e.g. heart beats, cord pulsations, breaths or definite movements of voluntary muscles, irrespective of their duration or placental/cord separation.

Fetal death is defined as absence of such signs in expelled/extracted products of conception and may be divided into—(a) *Early fetal deaths* or *abortions* (<20 weeks or <500 gm or <25 cm); (b) *Intermediate fetal deaths* (20–28 weeks; 500–999 gm or 25–35 cm), and (c) *late fetal deaths* (>28 weeks, >1000 gm or >35 cm). Intermediate and late fetal deaths are also termed *Stillbirths.*

Intrauterine period spans from the day of conception to the day of delivery (40 weeks or 280 days ±2 weeks). Accordingly, a newborn may be classified as *full term* (37–41 weeks), *preterm* (<37 weeks) or *post-term* (42 weeks). Babies born between 34–37 weeks are also termed as *Late preterms*, while those born before 28 week of gestation are considered as *extreme preterms*.

Intrauterine period includes two important phases in human life—e*mbryonic period* till first 8 weeks, predominantly characterized by organogenesis; and subsequent *fetal period* till birth, characterized by anatomical increase in body size and physiological maturation of various functions.

Neonatal period extends from birth to first 28 days of life and includes two important phases—*early neonatal period* from birth to 7th day and *late neonatal period* from 8th to 28th day.

Low birth weight: Since precise gestational assessment may be difficult in community practice, birth weight (BW) is often used as an indicator of neonatal maturity and health. A term newborn weighs ~3000 ±500 gm. Babies with BW of <2500 gm (up to 2499 gm) are termed *low birth weight* (LBW), while those weighing >3.5 kg are considered as *large for date*. Babies with BW of <1500 gm are also termed as *very low birth weight (VLBW)* and those <1000 gm as *extreme low birth weight (ELBW).*

Perinatal period: Late intrauterine period (>28 weeks or >1000 gm) and early intrauterine period (till 7th day) is considered as a continuum and together, termed '*perinatal period*'.

However, with increasing survival of extreme preterms in recent years, this critical period has been expanded to include a new category, i.e. *extended perinatal period*, from 22 week of gestation (or >500 gm) to 7 days of postnatal life.

12.2 PERINATAL HEALTH INDICATORS

Fetal and neonatal health may be considered as a reliable indicator of health standards in a community and usually measured in terms of following indicators:

Stillbirth rate (SBR) refers to *total number of stillbirths >28 weeks or 1000 gm/total live births 1000*. It is primarily an indicator of the quality of antenatal and obstetrical care in the community. Current SBR in India is estimated as ~ 3/1000 as per sample registration survey (SRS 2022), though seems to be much higher due to frequent non-reporting of stillbirths in rural areas. Congenital malformations and fetal distress are predominant causes of stillbirths.

Perinatal mortality rate (PNMR) is defined as *total number of late fetal deaths(LFD) >28 week + early neonatal death (END) till 7th day, expressed as a rate per 1000 live births per year*.

However as precise assessment of gestation is difficult, a more practical definition has replaced gestation with corresponding birth weight, i.e. 1000 gm, for international comparisons, as follows:

$$\text{PMR} = \frac{\text{LFDs + ENDs >1000 gm x1000}}{\text{Total live births >1000 gm}}$$

TABLE 12.1: Causes of perinatal mortality

- ***Antenatal:***
  - Maternal malnutrition
  - Maternal infections and illnesses
  - Local pelvic
  - Uterine diseases
  - Obstetric complications, e.g. eclampsia, APH
  - Fetal malformations
- ***Intranatal:***
  - Complicated
  - Obstructed labor
  - Birth asphyxia/injury
- ***Postnatal:***
  - Prematurity
  - Low birth weight
  - Neonatal infections
  - Congenital malformations
- ***Others***

APH: Antepartum hemorrhage

All still/live births < 28 weeks, 1000 gm or 35 cm length are excluded from numerator as well as denominator, due to unlikelihood of their survival.

Current status: Current PMR in India is 18/1000 live births (SRS 2022), being higher in rural areas than in urban areas. Despite declining trend in recent years, current PMR is still higher than that in developed countries.

Causes: About 60–70% of perinatal deaths relate to complications of LBW, followed by birth asphyxia and neonatal sepsis in the descending order **(Table 12.1)**. Congenital malformations are emerging as important cause of PMR, after control of other factors.

Prevention: PMR may be considered as single best indicator of fetal and neonatal health in a community. Important measures to reduce PMR include:

- *Pre-conceptional:*
  - Nutritional and health care of adolescents and reproductive-age females.
  - Appropriate birth spacing
- *Antenatal:*
  - Adequate antenatal care including TT immunization, nutritional counseling/ supplementation and iron/ folic acid supplements.
  - Early detection and treatment of maternal/ obstetrical complications
  - Identification of high-risk mothers and referral for institutional delivery
- *Peri-partum:*
  - Safe and clean delivery practices
  - Adequate fetal monitoring/neonatal resuscitation
- *Post-natal:*
  - Essential newborn care including breastfeeding
  - Identification of high-risk newborns with appropriate treatment/timely referral

Neonatal mortality rate (NMR) denotes *total number of neonatal deaths <28 days of life, expressed as a rate per 1000 live births per year,* calculated as follows:

$$\text{NMR} = \frac{\text{Total neonatal deaths >1000 gm} \times 1000}{\text{Total live births >1000 gm}}$$

NMR is further divided as ***Early neonatal mortality rate*** (ENMR), i.e. early neonatal deaths < 7 days/1000 live births) and ***Late neonatal mortality rate*** (LNMR), i.e. late neonatal deaths between 8th and 28th day/1000 live births.

Considering improved survival of extreme preterms/ low birth weights in recent years, a new term ***Extended neonatal mortality rate*** **(ExNMR)** is also in use to include all newborns >500 gm instead of 1000 gm for calculations.

Current NMR in India is 20/1000 live births including an ENMR of 15/1000 and LNMR of 5/1000 (SRS 2022). Throughout the world, NMR is higher in male newborns, perhaps due to biological fragility of male sex.

Low birth weight and related complications, birth asphyxia/injury, sepsis and congenital malformations are four major killers in newborn and important measures to reduce NMR are same as those for PNMR.

Low birth weight rate: Pre-conceptional and antenatal maternal health and nutrition are major determinants of birth weight, which is also influenced by frequency of intrauterine infections.

As all these factors are adversely prevalent in India, low birth weight rate is considered as important indicator of maternal and neonatal health. Current low birth weight rate in India is 18% (NFHS-5, 2021).

Maternal mortality rate (MMR) is an indicator of risk to the women's death due to puerperal causes, computed as total number of female deaths due to puerperal causes*/ total number of live births × 1000.

*Puerperal deaths include all female deaths due to obstetrical complications of pregnancy, childbirth/abortion or within 42 days of delivery/abortion (incidental/accidental deaths due to unrelated causes excluded).

Current MMR in India is 99/1000 live births (SRS 2022), highest in Uttar Pradesh and lowest in Gujarat.

Common causes of MMR in order of frequency include—(a) severe bleeding, (b) infection, (c) unsafe abortions, (d) eclampsia, and (e) obstructed labor. MMR is also related to many social factors, e.g. women's age, parity, birth interval, nutrition, and quality of antenatal care.

12.3 PRENATAL PEDIATRICS

Recent years have witnessed many advances in fetal diagnosis and therapeutics to ensure optimal fetal health and prevent neonatal complications. However, the most

important determinants of fetal health are maternal health, quality of antenatal care and timely identification of high-risk pregnancies to anticipate neonatal problems.

12.3.1 ESSENTIAL ANTENATAL CARE

Neonatal care begins since conception and antenatal care is an important element to ensure maternal, fetal and consequently, neonatal well-being.

Objectives: Antenatal care (ANC) aims to: (a) protect, promote and maintain maternal health, (b) identify high-risk mothers and plan appropriately, (c) teach her the elements of neonatal care, e.g. breastfeeding, and (d) sensitize her for family planning.

Schedule of care: Ideally, each mother should attend ANC clinic, once a month in first 7 months, twice a month in next two months and weekly thereafter. However, *minimum 4 visits are essential, during 3rd, 6th, 8th and 9th month.*

Components of ANC includes:

During first visits

- Registration
- Complete health and obstetrical history
- Detailed physical and obstetrical examination
- Investigations: Hb, urine, ABO/Rh type, VDRL, HIV (if consented) and USG (if possible).

During subsequent visits

- Physical revaluation: sp. for weight, BP and edema
- Obstetrical evaluation for fetal well-being
- Breast examination and counseling
- Investigations:
  - Hb, urine, others as necessary
  - USG in clinically abnormal cases
- Nutritional support
  - Dietary counseling/supplementation*
  - Iron and folic acid supplementation**
- Tetanus immunization***
- Counseling, regarding:
  - Basic child care and breastfeeding
  - Family planning
- Referral of high-risk mothers

*Additional 400 calories

**60 mg iron + 500 mg folic acid from 4th months onward

***Two doses of Td one month apart, last dose at least one month before delivery. Only one dose is necessary, if two doses were received within last 3 years during previous pregnancy.

Current status: NFHS-5 (2019–21) reveals that only 58.1% pregnant women in India receive recommended four antenatal care visits, while only 44.1% receive iron and folic acid supplements for minimum recommendations of 100 days during pregnancy. However, 92% mothers are protected for tetanus.

TABLE 12.2: High-risk pregnancies

Maternal (pre-conceptional) factors

- Age (<16 or >40 years)
- Parity (primi/grand multipara)
- Social factors, e.g. unwed mothers
- Malnutrition (weight <40 kg, height <140 cm)
- Anemia
- Chronic medical disease*
- Rh-negative blood group
- Bad obstetric history

Obstetric (antenatal) factors

- Multiple pregnancies
- Acute medical/surgical illnesses (or abd. trauma)
- *Infections:* TORCH infections, STDs
- Pregnancy induced hypertension, pre-eclampsia
- *Vaginal bleeding:* Placenta previa, APH
- Poly/Oligohydramnios
- *Fetal:* Abnormal maturity/lie, cong. malformations

*Diabetes, hypertension, cardiopulmonary or renal disease.
TORCH: Toxoplasmosis, rubella, cytomegalovirus, herpes simplex.

12.3.2 HIGH-RISK PREGNANCY

'At risk' approach is the most practical and cost-effective tool for antenatal care in resource-poor countries, which means *'Identification of high-risk mothers* **(Table 12.2)** *during antenatal period and arrange more skilled care for them, while continuing to provide appropriate care for other low-risk mothers'*.

High-risk pregnancies are often at-risk to terminate into abortions, stillbirths, prematurity, IUGR and congenital malformations. Common indicators of high-risk pregnancies may be recognizable even before the conception and these case should be managed only at centers where adequate facilities for fetal monitoring, neonatal resuscitation and critical care of sick newborn are available.

12.3.3 FETAL MONITORING

Maternal health is the most important determinant of fetal well-being, affecting its health in many ways **(Table 12.3)**. The term *'fetal monitoring'* refers to clinical, radiological, physiological and biochemical evaluation of fetus *in utero*, though last two steps are necessary only in selected cases. Important components of fetal monitoring are as follows:

I. Assessment of gestational duration by:

- *Last menstrual period* (LMP): Expected date of delivery (EDD) may be calculated by advancing LMP date with 9 months and 7 days.
- *Uterine fundal height* (UFH) is a reliable indicator of gestational length, except in last trimester. UFH is ~20 cm at 20 weeks and 28 cm at 28 weeks Disproportionately more UFH indicates multiple pregnancy, polyhydramnios, and fibroids.
- *Fetal events*, e.g. appearance of heart sounds (16–20 weeks) and *quickening* (18–20 weeks) are not very reliable indicators of gestational length.

TABLE 12.3: Effect of common maternal disorders and drug exposure on fetus and newborn

Malnutrition	IUGR	***Antidiabetic agents***	
Anemia	IUGR, early physiological anemia	Sulfonylurea	Hypoglycemia, ID (insulin safe)
Infections	IUGR, malformations (*see* Chapter 12.14.3)	***Antihypertensives***	
Systemic diseases		β blockers	IUGR, heart block, hypoglycemia
Hypertension	IUGR, birth asphyxia	Capto-/Enalopril	Oligohydramnios
Diabetes	Macrosomia, polycythemia, hypoglycemia	Thiazide diuretics	Thrombocytopenia
Iodine deficiency	Hypothyroidism, goiter, ID	***Antimalarials***	
Thyrotoxicosis	Hypothyroidism, Graves' disease	Quinine	Deafness, thrombocytopenia
Adrenal disease	IUGR, ? Addisons's crisis	Chloroquine	Safe for short course, deafness
Hyperparathyroid	Hypocalcemia	Primaquine	Hemolysis
Epilepsy	Birth asphyxia, drug-related	***Antitubercular drugs***	
SLE	Neonatal lupus	Streptomycin	Deafness, nephrotoxicity
ITP	Neonatal thrombocytopenia	Ethambutol	Minor malformations
Myasthenia	Neonatal myasthenia	INH/Rifampicin	Safe, ? hepatotoxicity.
Obstetric problems		***Anti-thyroid agents***	
APH	IUGR, birth asphyxia	Methimazole	Hypothryroidism, goiter
Polyhdramnios	Anencephaly, gut ectasias, e.g. TOF	Propylthiouracil	Relatively safe, goiter
Oligohydraminos	Renal anomalies, deformation sequence	Radio-Iodine	Hypothyroidism, brain damage iodides congenital goiter, hypothyroidism
Rh –ve mother	Hemolytic disease of newborn	***Anti-cancer agents***	
Substance abuse		Anti-folates	NTDs
Smoking	IUGR	Cyclophosphamide	Congenital malformations
Alcohol	IUGR, ID, *fetal alcohol syndrome*[1]	Radiation	ID, microcephaly
Cocaine	Cerbrovascular strokes, withdrawal	***Hormonal preparations***	
IVDrug abuse	Infections, e.g. HIV, HBV	Oral contraceptives	Amb. genitalia, gynecomastia, limb anomalies
Drug exposure ***Antibiotics***		Progesterone	Masculinization, hypospedias
		Steroids	Cleft palate, ? adrenal crisis
Peniciilin	Rash	Oxytocin	Hyperbilirubinemia
Tetracycline	Dental staining, cataract, poor bone growth	***NSAIDs***	
Sulfa drugs	Rash, hemolysis, hyperbilirubinemia	Salicylates	Rash, bleeding, hyperbilirubinemia
Anticovulsants:		Ibuprofen	Oligohydramnios
Phenobarbitone	Drowsiness/resp depression/withdrawal	Indomethacin	IUGR, bleeding
Phenytoin	IUGR, *fetal hydantoin syndrome*[2] vitamin K def. bleeding, ? neuroblastoma	***Miscellaneous***	
Diazepam	Drowsiness, hyperbilirubinemia, apnea	Clomiphene	NTDs, multiple births, Down syndrome
Valproate	Facial anomalies, NTDs, ID	Lithium	CHDs (Ebstein anomaly), goiter
Carbamazepine	NTDs	Lead/Mercury	Neurotoxicity, ID
		Mag sulfate	Hypotonia, resp. depression
		Thalidomide	Limb defects
		Theophylline	Irritability, ? neonatal seizures
		Vitamin A excess	NTDs and other malformations
		Vitamin D excess	Supravalvular aortic stenosis, others

IUGR: Intrauterine growth retardation; **ID:** Intellectual disability; **NTDs:** Neural tube defects; **TOF:** Tracheoesophageal fistula; **ITP:** Immune thrombocytopenia; **APH:** Antepartum hemorrhage

[1]***Fetal alcohol syndrome:*** Facial dysmorphism, IUGR, developmental delay, learning/behavioral problems

[2]***Fetal hydantoin syndrome:*** IUGR, facial dysmorphism, hypoplastic nails, mild MR

- *USG assessment* is most accurate method for dating gestation in normal fetus. Different fetal parameters are used in different stages of gestation—crown-heel length (up to 12 weeks), bi-parietal diameter (up to 28 weeks) and femoral length beyond this age.

II. Assessment of fetal growth by:

- *Maternal weight gain:* Steady maternal weight gain indicates satisfactory fetal growth. Average healthy Indian woman gains ~ 9–10 kg in pregnancy.
- *Serial abdominal girth* increase of ~1 cm/week from 20th week onwards, indicates normal fetal growth.
- *Serial increase in UFH* is a reliable indicator of adequate fetal growth, when compared with gestation-parto-graphs (fetal growth charts).
- *USG assessment* is a non-invasive and accurate tool to identify intrauterine growth retardation (IUGR) apart from other obstetrical abnormalities, e.g. multiple pregnancies, congenital anomalies, abnormal placental morphology, presence of poly/oligohydramnios, etc. A Bi-parietal diameter <8.5–9.0 cm at full term indicates IUGR. However, *Fetal head/thorax* or *head/abdomen ratio* are more reliable, as somatic growth is more affected in IUGR.

III. Assessment of physiological maturity of fetus is indicated in expected preterm deliveries. It requires amniocentesis with following tests in amniotic fluid (AF):

- Lung surfactant maturity, e.g. L:S ratio (>2)
- Amniotic fluid optical density (> 0.15)
- Renal maturity (AF creatinine > 2 mg/dl)
- Skin maturity by AF cytology (> 20% orange staining cells).

IV. Detection of congenital anomalies is based on:

- Routine screening, e.g. USG or serology.
- Genetic studies, e.g. karyotyping in select cases.
- Amniotic fluid biochemistry:
  - *Raised α-fetoprotein* levels (14–16 weeks) in neural tube defects, exomphalos, gut atresia.
  - *Raised optical density difference* >0.1 in Rh-hemolytic disease with severe hemolysis.
  - *Raised pregnanediol* levels in congenital adrenal hyperplasia
  - *Low human chorionic gonadotropin* levels indicate threatened abortion; *elevated levels* in Down syndrome and molar pregnancy.
  - Specific enzyme assays in suspected IEMs.

α-fetoproteins (AFP) is a glycoprotein, produced by yolk sac and fetal liver from 2nd months onwards. Production peaks at ~14th week, followed by gradual decline with advancing gestation. After birth, AFP production ceases within a few days except in newborns with liver disease. Fetal AFP can cross the placenta (detectable in maternal serum) as well as also appears into amniotic fluid due to shedding of fetal skin.

Maternal *or* amniotic fluid AFP levels are useful biochemical markers of fetal well-being. Normally, maternal serum AFP is ~25 ng/ml at 16th week (optimal time for screening) and rises by ~15% per week till 30th weeks, followed by gradual decline. AFP levels are elevated in neural tube defects, liver defects, some congenital malformations and multiple pregnancies, while reduced in Down syndrome.

V. Assessment for fetal distress: Although clinical monitoring of fetal heart sounds and movements is the simplest tool to assess fetal well-being, following evaluation may be necessary in selected cases to decide the need for immediate intervention:

a. *Indicators of placental dysfunction* (maternal sample)
   - S. placental lactogen (<4 µg/ml after 30 weeks)
   - Plasma/urine estriol (>30% drop from earlier values)

b. *Tests for uteroplacental unit:*
   - *Non-stress monitoring (NST),* i.e. simultaneous recording of Fetal heart rate (FHR), uterine contractions and fetal movements. Acceleration of FHR by >15 bpm *or* for >15 seconds after fetal movement, at least twice in 20 minutes, indicates adequate utero-placental function.
   - *Oxytocin challenge test* to assess effect of oxytocin stimulated uterine contractions on FHR. Persistent slowing of FHR after uterine contraction (*late deceleration*) indicates placental insufficiency.

c. *Direct indicators of fetal distress:*
   - Fetal heart monitoring (absent FHS)
   - Fetal activity record (less/absent movements)
   - Fetal biophysical profile (USG based)
   - Fetal scalp blood sampling for blood gas analysis

Fetal biophysical profile is the most accurate non-invasive test for fetal well-being, using five USG-based fetal parameters—(i) posture, (ii) breathing movements, (iii) gross body movements, (iv) reactive heart rate and (v) volume of amniotic fluid. Each parameters is scored as 2 normal or 0 as abnormal. A combined score of 6 or less indicates *chronic fetal asphyxia.*

Fetal scalp blood sampling for blood gas analysis under endoscopic guidance, is most reliable but invasive test. A scalp pH of <7.1 indicates severe hypoxia and need for immediate delivery.

12.3.4 FETAL THERAPY

Fetal therapeutics is still in fetal stage, though rapid advances in antenatal diagnosis have opened new vistas to prevent or manage fetal disease *in utero*. These interventions may be divided into three categories: (a) preventive interventions in high-risk pregnancy, (b) medical interventions in prenatally-diagnosed cases, and (c) surgical interventions in congenital malformations.

TABLE 12.4: Prenatal interventions (Fetal therapy)

Disorders	*Prenatal intervention*
a. Rec. fetal loss/LBW	Low-dose aspirin
b. Neurological	
– IVH/PVH	Phenobarbitone
– Neural tube defects	Folic acid supplements
c. Respiratory	
– Hyaline membrane disease	Dexamethasone
– Fetal hypoxia	Oxygen, positioning
– Meconium aspiration	Amnioinfusion
d. Hematological	
– Rh-HDN	Umb. exchange transfusion
– Fetal ITP	IVIG, IU platelet infusion
– Thalassemia	Fetal stem-cell transplant
e. Intrauterine infections	
– HIV	LSCS, ART to mother
– Tuberculosis	Anti-tubercular therapy
– Syphilis	Penicillin
– Toxoplasmosis	Spiramycin/pyrimethamine
– CMV	Ganciclovir (via umb. vein)
f. Endocrinal/metabolic	
– CAH	Dexamethasone
– IEMs	Megavitamin therapy
g. Obstetric complications	
– Meconium staining	Amnio-infusion
– Premature labor	Tocolytics, Mg sulfate
– Poly/oligohydramnios	Amnioreduction/infusion
h. Surgical interventions	
– Hydrocephalus	Fetal ventricular tap
– Obstructive uropathy	Fetal urinary shunts
– Chylothorax/hydrops	Thoraco/abdominocentesis
– Multiple pregnancy	Fetal reduction

IVH/PVH: Intraventricular/periventricular hemorrhage, **HDN:** Hemolytic disease of newborn, **ITP:** Immune thrombocytopenic purpura, **ART:** Anti-retroviral therapy, **CAH:** Congenital adrenal hyperplasia, **IEM:** Inborn errors of metabolism, **LBW:** Low birth weight.

Table 12.4 enlists some disorders for which fetal therapy is possible or will be possible shortly, along with modes of intervention. However, some specific strategies are as follows:

Steroids in prematurity: Administration of IM Dexamethasone (Four doses of 6 mg at 12 hourly interval) or IM betamethasone (Two doses of 12 mg at 12 hourly interval), at least 24 hours before delivery is an established intervention in mothers, likely to deliver <34 weeks of gestation. This simple measure reduces the risk of hyaline membrane disease (HMD) and intraventricular hemorrhage (IVH) in preterms by ~30–50%. However, it is contraindicated in presence of chorioamnionitis.

Phenobarbitone in Rh-isoimmunization: Administration of PO phenobarbitone (60 mg OD) for 2 weeks before anticipated time of delivery reduces the severity of neonatal hyperbilirubinemia and need for exchange transfusion. Phenobarbitone therapy has also been claimed to reduce risk of IVH/PVH in preterms, though not supported by evidence.

Folic acid supplements in neural tube defects: In mothers with history of previous birth with neural tube neural tube defects, PO folic acid 0.4 mg (4 mg OD for secondary prevention) once a day from two month before the expected conception to the end of first trimester, reduces the risk of recurrence > 50%.

Anti-retroviral therapy in HIV +ve mothers: Risk of perinatal HIV transmission from mother to the baby is known to reduce from 30–40% in untreated cases to <5% with appropriate antiretroviral therapy to mother, irrespective to her own health.

Intrauterine blood transfusion in Rh-HDN, via cordocentesis, may be life-saving in severe anemia with fetal hematocrit <20%. Repeated simple or exchange transfusions are often necessary till 32 weeks of gestation, followed by elective preterm delivery. In non-immune hydrops, IV albumin infusion may be used to prevent further fluid exudation.

Steroid therapy in congenital adrenal hyperplasia (CAH), with PO dexamethasone (1 mg OD) is indicated throughout pregnancy from 10th week onwards in prenatally detected CAH or history of previous CAH delivery, to prevent virilization of fetus.

Magnesium sulphate in mother undergoing preterm labor given as 4 gm/kg IV loading dose over 30 minutes followed by 1 gm/hour for 24 hours is known to reduce the risk of cerebral palsy and developmental delay.

Megavitamin therapy in inborn errors of metabolism may be useful to prevent mental retardation in prenatally detected cases of methyl-malonic acidemia (IV vitamin B_{12} 5 mg OD) or multiple carboxylase deficiency (PO biotin 10 mg OD), when given in last trimester.

Steroid therapy in maternal immune thrombocytopenia (ITP), during last 2 weeks may prevent fetal isoimmunization. However, prenatally detected isoimmune thrombocytopenia needs platelet infusions and IVIG therapy via cordocentesis to prevent severe fetal hemorrhage.

12.3.5 MULTIPLE PREGNANCY

Multiple pregnancy is an important obstetrical risk factor for fetal loss or neonatal morbidity/mortality, with an incidence of ~1:80 livebirths (for twins) and ~ 1:1000 (for triplets), in India. However, true incidence of twin *conceptions* is much higher (2–3% on USG at 12 weeks), as many of them end in fetal loss or disappearance of one fetus (*Vanishing twin syndrome*). Incidence of multiple pregnancies seems to be rising in recent years, due to increasing interventions for infertility, e.g. ovarian stimulant drugs or *in vitro* fertilization.

Types: Multiple pregnancies may be:

- *Polyovular* (Dizygotic), with release and fertilization of two (or more) different ova at the same time, each with its own chorion and amnion (*dichorionic, diamniotic*). Dizygotic twins are of different sex and blood group in 50% cases.
- *Mono-ovular* (Monozygotic), with fertilization of a single ova but splitting of blastocyst in early phase to develop separately as two fetus. 75% of monozygotic twins share common chorion (*monochorionic*), though almost all of them have separate amnion (*diamniotic*). Monozygotic twins are essentially of same sex, blood group and grossly similar, if not identical, features.

Splitting of blastocyst in late stages may lead to *conjoined or Siamese twins* (~1:50,000 live births), which are usually females and joined to each other at thoraco/abdominal region (thoraco/omphalopagus; commonest), head (craniopagus, rarest) or other sites (incomplete duplication).

Risk factors: While risk factors for mono-ovular multiple pregnancies are unclear, poly-ovular pregnancies are more common in: (a) elderly or multiparous mothers, (b) family history of multiple pregnancy, (c) conceptions after infertility interventions, and (d) women with high gonadotropin levels.

Complications: Apart from frequent abortions or stillbirths, multiple pregnancies are associated with ~3–4 times higher risk of neonatal mortality/morbidity due to various complications **(Table 12.5)**, most important being twin-to-twin transfusion.

Twin-to-twin transfusion (*Fetal transfusion syndrome*) mainly occurs in monochorionic twins, due to common placenta. Artery from one fetus (donor) may acutely or chronically deliver blood into vein of other fetus, leading to *severe anemia, hypovolemia and low birth weight in the donor* and *plethora, polycythemia, hypervolemia and hydrops in the recipient*. Generally, a difference of >5% in Hb and 20% in weight between two fetuses indicates twin-to-twin transfusion. Death of the donor fetus generates plenty of fibrin thrombi, which may be passed-on to surviving fetus with consequent DIC.

Management of multiple pregnancies involves early prenatal diagnosis and timely referral to equipped centers. *Selective fetal reduction* with transabdominal injection of potassium chloride may be required in numerous multiple gestations (3 or more).

Postnatally, all twins should be closely monitored till 24–48 hours for late problems, e.g. hypoglycemia, respiratory distress, anemia, polycythemia, etc. Twin-to-twin transfusion may require immediate blood transfusion to the donor and partial exchange in the recipient.

Prognosis: Although perinatal mortality is ~4-times higher in twins, survival among live born twins is relates to birth weight and gestation (comparable with singletons). Usually, first-born twin is smaller and at-risk for hypoglycemia while second twin has higher risk of birth asphyxia and respiratory distress syndrome. Concordant illnesses, e.g. hyaline membrane disease or infections are common in twins and the weight difference tends to disappear by 4–6 month of age.

TABLE 12.5: Complications of multiple pregnancies

- **Due to uterine overcrowding**
  - Low birth weight
  - Prematurity
  - Positional deformities, e.g. CDH
- **Due to shared blood supply**
  - Twin to twin transfusion
  - Intrauterine hypoxia
  - Vascular anomalies
- **Obstetrical problems**
  - Polyhydramnios
  - Abnormal placenta/antepartum hemorrhage
  - Premature rupture of membranes
  - Abnormal lie (obstructed labor)
- **Postnatal complications**
  - Birth asphyxia
  - Severe anemia in donor twin
  - Polycythemia in recipient twin
  - Hypoglycemia
  - Respiratory distress syndrome

CDH: Congenital dislocation of hip

12.4 DELIVERY ROOM CARE AND NEONATAL RESUSCITATION

Safe delivery is a critical component of *maternal and child health care*, to ensure smooth and uneventful childbirth as well as maternal well-being. Depending on the anticipated risk of complications, a delivery may be planned at peripheral health centers or referral centers.

Delivery room care may be divided into two components: (a) *basic or essential delivery room care* to all newborns, and (b) *neonatal resuscitation*, an emergency that may arise in any, specially high-risk newborns.

12.4.1 ESSENTIAL DELIVERY ROOM CARE

Basic delivery room care begins even before the birth. Important components of essential delivery room care are as follows:

Step I. **Pre-delivery review of antenatal health records:** Although the need for neonatal resuscitation may arise unexpectedly, it is possible to identify many high-risk pregnancies **(Table 12.2)** by review of antenatal records and refer them to adequately equipped centers.

Step II. **Pre-delivery preparations in labor room** to receive the baby and resuscitate, if needed. These include:

- All normal deliveries should be attended by a *trained medical or health attendant*. However, an expert pediatrician should always be stand-by, in case of unexpected emergencies.

- Labor room temperature should be ~25–28°C, to avoid sudden heat loss at birth. A commercial or indigenous-made warmer should be switched-on at least 15 minutes before the expected delivery.
- A pre-warmed baby receptacle (tray), lined with clean linen should be available to receive the baby after delivery, along with enough supply of extra linens.
- Availability of essential resuscitation equipment and drugs **(Table 12.10)** should be ensured, *and* in working condition.
- Universal safety precautions for infection control are necessary to protect not only the baby but also the health-staff. ***6 Cs*** *to ensure minimal asepsis during the delivery include—**C**lean hands with quality hand washing and use of gloves, **C**lean surface to receive the baby, **C**lean perineum, **C**lean blade to cut the cord, **C**lean clamp/ tie to tie the cord, and **C**lean, dry cord with no local application.*

Step III. **Intra-partum interventions** include:

- *Clamping of the umbilical cord*. Normally, the cord should be cut after 30–60 seconds of delivery by a sterile blade, leaving at least 2–3 cm of umbilical stump and tied properly to avoid slipped-ligature and bleeding.

  Delayed cord clamping is recommended in all stable term and preterm babies, who cried immediately after birth to improve hemoglobin status and iron stores. It is specially recommended in IUGR and anemic babies.

  Early cord clamping is recommended in asphyxiated newborns in need for immediate resuscitation, Rhesus isoimmunization and in first-born twin to minimize twin-to-twin transfusion.
- Collection of cord blood sample for grouping/cross matching and screening investigations for intrauterine infections or metabolic disorders, as per local protocol.
- Early skin-to-skin contact and *breast-crawl* to promote early breastfeeding and reduce the risk of hypothermia.
- Inform the mother about baby's gender and well-being.

Step IV. **Receiving the newborn:** Prevention of sudden hypothermia at birth is the most important component of immediate newborn care. As soon as the cord is cut, baby should be received in the pre-warmed tray, transferred under the warmer and wiped gently to clean and dry. No extra efforts should be made to remove the vernix, which protects against hypothermia. Wet linen, after wiping the baby should be discarded and changed.

Step V. **Ensuring the airway patency**, by:

- *Cleaning of oral cavity* for mucus, blood, meconium, etc. manually, by clean gauze piece;
- *Oropharyngeal suction* is not recommended in newborns who start breathing on their own after birth, while in others a low-pressure suction with an *Delee's* oral mucus extractor **(Fig. 31.9)** may be used to clean the airways. Vigorous suction must be strictly avoided to prevent trauma and reflex bradycardia/apnea.
- *Positioning* the baby in supine position with a rolled towel under the shoulders to prevent hyperextension/flexion of neck **(Fig. 12.2)**.

Step VI. **Stimulating the breathing**: While most newborns cry immediately after birth or as soon as the air-passage is cleaned, *gentle physical stimulation* by flicking on soles/rubbing the body may be necessary in others to stimulate first cry. Inverting the baby or *vigorous back-slapping should never be attempted.*

Step VII. **Quick clinical assessment** for resuscitation needs, A*pgar score*, lethal congenital anomalies, birth injuries, gestational age and other complications. Apgar scoring should also be repeated after 5 minutes to predict future neuro-developmental course.

Orifice counting and patency check—congenital anomalies tend to concentrate around natural orifices, e.g. nose, oral cavity, anus, urethral meatus and ears. Since many of them are serious or associated with internal malformations, it is advisable to quickly check these orifices for external abnormality, though there is no need to check the patency routinely with catheter. Esophageal patency must be checked before first feed in high-risk newborns with polyhydramnios, single umbilical artery, other congenital anomalies or frothing.

Stomach wash is recommended only in babies with-(a) cesarean delivery, (b) severe asphyxia, (c) meconium staining.

Step VIII. ***Cleaning of the baby*** must be limited to drying with a clean sterile cloth and gentle removal of blood and meconium. Vernix protects the skin and helps to maintain body temperature and hence, should not be removed.

Step IX. Weighing, tagging (identification) and gender assignment.

Step X. **Initiation of breastfeeding:** In all normal newborns, breastfeeds should be started as early as possible, usually within ½ hour of delivery and in the labor room itself. Though milk output at this time may be negligible, early feeding ensures successful lactation and emotional mother-baby bonding.

Step XI. **Examination of umbilical cord and placenta:** Essential delivery room care is not complete without examination of umbilical cord and placenta **(Table 12.6)**. Single umbilical artery (normally two), is associated with congenital malformations in 10–20% cases.

12.4.2 NEONATAL RESUSCITATION

While most newborns do not require any resuscitation beyond the maintenance of temperature, suctioning of airways and mild stimulation, adverse perinatal events, e.g. birth asphyxia may preclude smooth neonatal cardiopulmonary transition, unless assisted.

TABLE 12.6: Placental exam and its significance

Normal

Placental weight : 400–500 gm
Umblical cord length : 30–50 cm

Abnormal placenta

- *Large size:* IU infections, polyhydramnios, Rh-HDN
- *Small size:* IUGR, maternal malnutrition
- *Type:* Monozygous *vs* Dizygous (in twins)
- *Dull/milky:* IU sepsis
- *Grayish/yellow:* Meconium deliveries, Rh-HDN
- *Nodular:* Oligohydramnios
- *Multiple infarcts:* IU hypoxia, post-maturity
- *Retroplacental hemorrhage:* Severe anemia
- *Histological examination* for tubercles, malaria

IUGR: Intrauterine growth retardation, **Rh-HDN:** Rh-hemolytic disease of newborn

TABLE 12.7: Resuscitation alert (high-risk delivery)

- *High-risk pregnancy* ***(Table 12.2)***

+

- Pre-term/post-term delivery
- Malpresentation, e.g. breech, transverse, etc.
- Obstructed/prolonged labor
- Signs of fetal distress:
  - Meconium stained liquor amnii
  - Altered fetal heart sounds/movements
  - Abnormal tests for fetal well-being, e.g. NST
- Premature rupture of membranes
- Cord prolapse
- Cord around the neck
- Interventional delivery: LSCS, forceps, etc.
- Low Apgar score at 1 minutes (<4)

NST: Non-stress test

Primary goal of neonatal resuscitation is to *establish adequate respiration and cardiac output in asphyxiated newborns at birth*, to prevent early neonatal morbidity/mortality as well as late sequelae of hypoxic-ischemic damage.

Pathophysiology: Asphyxiated babies, whether *in utero* or *post-birth*, respond to the oxygen deprivation in a fairly constant sequence, i.e. development of primary apnea followed by terminal apnea.

Primary apnea is the immediate and transient response to oxygen deprivation, usually preceded by a short period of rapid breathing, followed by *sudden cessation of breathing*, falling heart rate (usually *>100/ min*) but with *maintained blood pressure*. These cases respond well to gentle tactile stimulation with re-initiation of breathing.

Terminal apnea is the response to continued asphyxia, after a brief period of recovery from primary apnea, characterized by *gradual cessation of breathing* after few gasps with significant drop in *heart rate (<100/min)*, *blood pressure* and *unresponsiveness* to stimuli. These patients do not respond to tactile stimulation and need more intensive resuscitation.

In cases of fetal hypoxia, one or both phases may pass *in utero* and the baby may be born in primary or terminal apnea, which is difficult to distinguish and it is safer to assume that s/he is terminal apnea and needs full resuscitation.

Other important considerations in resuscitation of newborns are:

- High airway resistance and pulmonary vascular resistance, due to poor lung expansion in first few breaths,
- Consequent hypoxia and acidosis leading to poor pulmonary perfusion and myocardial dysfunction, and
- Redistribution of blood flow from non-vital to vital organs (diving-in reflex) leading to multi-organ dysfunction .

Resuscitation alert: Although the need for resuscitation may arise unexpectedly, it is often possible to identify high-risk cases on the basis of proper history, review of previous maternal records and monitoring of the obstetrical course **(Table 12.7)**.

Pre-delivery preparations: All high risk deliveries must be attended by an adequately-trained pediatrician, preferably with an assistant. As soon as the need for neonatal resuscitation is felt, a pre-arranged plan of action should be activated to ensure presence of the trained staff and availability/ functioning of resuscitation equipment/drugs, etc. **(Table 12.8)**.

TABLE 12.8: Resuscitation equipments and drugs

- Pre-warmed resuscitation tray
- Pre-warmed warmer/resuscitation trolley
- Suction equipments
  - Low-pressure suction machine
  - Delee' mucus extractor
  - Suction catheter 10,12,14 Fr.
- Oxygen source with humidification and flow gauze
- Bag and mask ventilation
  - Resuscitation (AMBU) bag (250–500 ml)
  - Neonatal face masks
- Intubation equipments
  - Laryngoscope with straight blades (size 0, 1)
  - Endotracheal tubes (size 2.5, 3, 3.5, 4) with adopter/stylet
  - Nasogastric tube
- Medications
  - Umbilical catheters 3.5–5 Fr
  - Syringes and needles
  - Pre-filled Adrenaline (1:10000)
  - IV fluids: Normal saline
  - Naloxone hydrochloride
- Others
  - Timer
  - Linen/ gauze
  - Gloves
- Working electrical points
- Adequate manpower

TABLE 12.9: TABC of neonatal resuscitation

Temperature control
- Warmth under radiant warmer
- Drying the baby
- Removal of wet linens

Airway patency by
- Proper positioning
- Oropharyngeal suction
- Endotracheal suction

Breathing by
- Tactile stimulation
- Positive pressure breathing (PPV)
- Endotracheal intubation

Circulation by
- Chest compressions
- Medications

Principles: Basic principles of neonatal resuscitation include measures to restore and maintain four cardinal body functions—temperature, airway, breathing and circulation, often referred as **TABC** *of resuscitation* **(Table 12.9)**.

Protocol: Current neonatal resuscitation program (NRP), based on American Academy of Pediatrics *recommendations 2020,* propose a step-wise algorithm, as follows **(Fig. 12.1)**:

Step I. Initial assessment, as soon as the baby is delivered, aims to identify babies who need resuscitation, based on three simple parameters: (*a) gestation, (b) tone,* i.e. *posture and movements, and (c) breathing or crying.* No further resuscitation is required if the baby is full term, breathing/crying and moving with flexed posture, except basic delivery room care (Ch 12.4.1).

Babies who are preterm, flaccid or not breathing/crying, need immediate resuscitation with following steps. In them, cord should be clamped and cut as soon as possible, without waiting for minimum 30 seconds (Early cord clamping).

Step II. Initial steps in resuscitation aim to prevent hypothermia, clear the airways and stimulate breathing, by following interventions termed *"initial steps"*, which should be completed within 30 seconds.

a. ***Warm:*** Place the baby under a radiant warmer.
b. ***Dry*** with pre-warmed linens and remove wet linens.
c. ***Stimulate*** by gently rubbing the trunk, back and extremities to stimulate breathing/crying. Do not shake or rub vigorously.
d. ***Position*** the baby in supine position with neck slightly extended (sniffling position) to bring posterior pharynx, larynx and trachea in line and facilitate breathing. To maintain this position, a rolled towel may be placed under the shoulders **(Fig. 12.2)**.
e. ***Clear airway*** by wiping of the nose/mouth, though a gentle suction with a disposable mucus extractor or a 12–14 Fr. catheter may be required to clear the airway in some newborns. Head may be turned to one side to clear secretions in babies with copious secretions. Essentials of a good suction are as follows:
   – Mouth should be suctioned before the nose (M before N);
   – Suction pressure should never exceed 100 mm Hg (130 cm H_2O);
   – Suction catheter should not be inserted too deep, to avoid vagal stimulation and

Intrapartum suction or postnatal tracheal suction in non-vigorous babies with meconium stained amniotic fluid is no longer recommended.

Step III. Re-evaluation: After *initial steps*, baby must be re-assessed at 30 seconds. Approximately 60 seconds (*"the Golden Minute"*) are allotted for completing the initial steps, re-evaluation and beginning the breathing support, if required.

Current guidelines recommend use of two parameters-heart rate (HR) and respiration at 30 seconds, to decide further resuscitation measures, as well as observation for color or monitor for target SpO_2 **(Fig. 12.1)**.

Auscultate the heart or palpate for cord pulsations to assess the HR, which should be counted for 6 seconds multiplied by 10 to arrive at HR/min. Simultaneously, color should be observed over mucus membranes, e.g. tongue to detect central cyanosis (acrocyanosis has no significance in resuscitation).

No further intervention is required in babies with HR >100 and breathing normally, except to ensure warmth, clear airways and monitoring. Other cases need further resuscitation as follows:

– Babies with labored breathing and/or persistent central cyanosis must be provided supplemental oxygen at the rate of 5 L/min with a face mask, along with SpO_2 monitoring.
– Babies with: (a) apnea or gasping respiration, (b) HR < 100 or (c) persistent cyanosis on 100% oxygen must be started on positive pressure ventilation without delay (within the golden minute).

Step IV. Positive pressure ventilation (PPV) should be initiated without delay for indications as above, using a self-inflating resuscitation bag (ambulatory breathing unit or AMBU bag) with face mask **(Fig. 12.3)**. Resuscitation bag usually delivers 21% oxygen at room air without oxygen connection, 40–50% at an oxygen flow rate of 4–5 L/min with no reservoir, and 90–100%, if used with a reservoir. *PPV is contraindicated in cases with diaphragmatic hernia*, but may be used in those with potential meconium aspiration.

Some important considerations for bag and mask ventilation in NRP are as follows:

- *Appropriate position* of the head with slight extension to ensure clear airways.
- *Appropriate size of resuscitation bag (250–500 ml)*

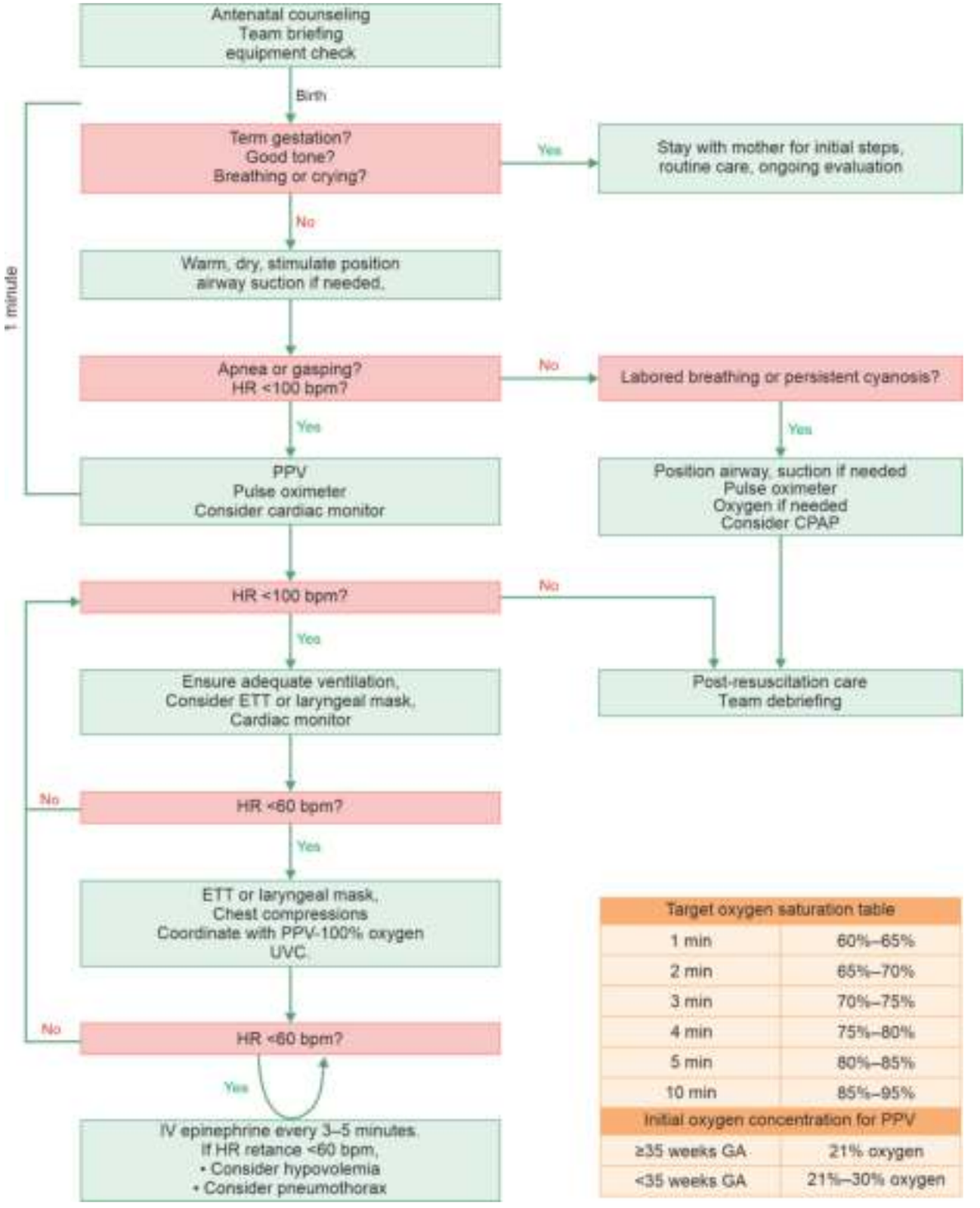


Fig. 12.1: Neonatal Resuscitation Algorithm.
Adopted from: American Heart Association 2020 guidelines.

- *Appropriately fitting face mask to* cover the nose and mouth but not the eyes.
- *Appropriate* FiO_2 with room air in babies >35 weeks and 21–30% for preterms <35 weeks, though should be adjusted later according to SpO_2 monitoring for target values, to the maximum of 100% in case of no improvement in 90 seconds.
- *Appropriate ventilation pressure,* applied by fingers and not the hands. First few breaths require higher bagging pressure (30–40 cm H_2O) to expand collapsed lungs,

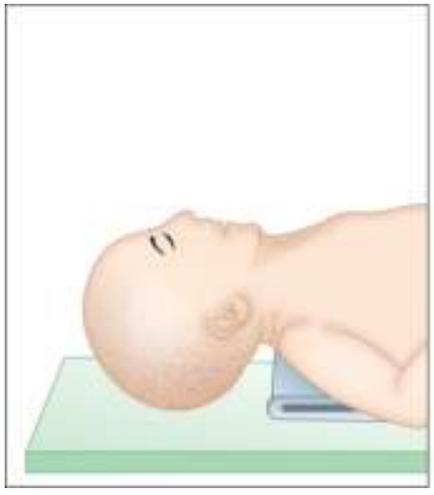


Fig. 12.2: **Proper sniffling positioning for resuscitation.**

Fig. 12.3. **Correct application of face mask (covering mouth, nose and chin but not eyes).**

but subsequent pressure should not exceed 20–25 cm H_2O, to prevent barotrauma.

- *Appropriate ventilation rate* of 40–60/min, following a *squeeze, one, two three, squeeze…* sequence.
- *Successful bag and mask ventilation* is indicated by: (a) good chest rise, (b) symmetric air entry, (c) disappearance of cyanosis, and (d) increase in heart rate. In absence of these indicators with poor chest wall movement and absence of breath sound on auscultation, following reasons and *Corrective steps* should be considered: (a) inadequate seal (reapply mask), (b) blocked airways (reposition the head, clear secretions by suction, and ventilate with mouth slightly open), (c) inadequate pressure (increase pressure slightly).
- PPV may also cause gastric distension due to swallowed air, which can be prevented by insertion of an orogastric tube in stomach, if PPV is required for >2 minutes.

After 30 seconds of effective PPV, baby should be evaluated again for HR to make following decisions:

- Babies with HR >100/min should be continued on PPV with monitoring. As the spontaneous breaths start, rate must be reduced accordingly and PPV can be stopped when baby has good respiratory efforts with HR persistently > 100/min.
- Babies with HR <100 but > 60, who do not improve despite increasing FiO_2 must be considered for endotracheal intubation.

Step V: Endotracheal (ET) intubation is indicated only in small proportion of cases, with: (a) poor response to PPV (HR < 100 and not increasing) after 30 seconds, (b) suspected diaphragmatic hernia, and (c) extreme preterm infants, who are also going to need surfactant therapy. Essentials of good ET intubation include:

- Appropriate size of laryngoscope blade, i.e. straight-blade of size 0 (preterms) or 1 (term).
- Appropriate size of ET tube, i.e. 2.5 for <1 kg; 3 for 1–2 kg; 3.5 for 2–3 kg and 4 for >3 kg.
- Appropriate depth of ET tube, calculated as distance from tip of the nose to tragus + 1 cm.
- Appropriate skill to perform, with each attempt not exceeding >20 seconds. Intermittent bag/mask ventilation for 30 seconds must be given before the next attempt, to prevent hypoxia.
- Correct placement of the ETT must be confirmed by bilaterally equal air entry and chest movement.

A laryngeal mask may be considered as an alternative to ETl intubation in newborns >34 weeks, if it is not feasible or unsuccessful.

Persistent of HR <60 despite effective ET intubation needs to begin with chest compressions and consider medications.

Step VI. Chest compressions aim to improve mechanical pumping of the blood to vital organs, indicated if HR *remains <60/min despite 30 seconds of PPV*. Chest compressions should be stopped once HR exceeds 60/min.

Chest compressions help to mechanically pump blood to vital organs and restore some perfusion and should always be accompanied with PPV.

Chest compressions involve compressing the lower-third of sternum by *two-finger technique* or *by thumb technique* **(Fig. 12.4)**, interspersed with PPV, at a ratio of 3:1 (90 compressions:30 breaths). Essential features of good chest compressions are:

- *Compression rate:* ~ 90/min (with PPV 30/min).
- *Depth:* ~ 1/3rd of chest's antero-posterior diameter.
- Relaxation time more than compression time.

Fig. 12.4: External cardiac massage in newborns: (A) Two-finger technique; (B) Two-thumb technique.

Potential complications include rib fractures, pneumothorax and liver injury. Chest compressions should be discontinued once the HR exceeds 60/min, continuing with PPV at the rate of 40–60/min.

Persistence of HR < 60 despite 60 seconds of chest compressions ad effective PPV, indicates need for medications.

Step VII. Medications have limited role in resuscitation, except epinephrine and volume expanders in some cases. Umbilical vein cannulation is preferred for quick IV access to deliver these medications, as follows:

- *IV Adrenaline* (1:10000) 0.1–0.3 ml/kg, is indicated if HR remains <60/min after 60 seconds of effective PPV and chest compressions and may be repeated every 3–5 minutes. It may also be given intratracheally after diluting in 1–2 ml of normal saline, if IV access is not available.
- *IV normal saline or Ringer lactate* 10 ml/kg, as volume expander in newborns with hypovolemic shock (feeble peripheral pulses despite adequate HR and ventilation).

There is no role of atropine, naloxone and steroids etc during neonatal resuscitation.

Step VIII. Consolidation phase, after initial recovery, involves shifting the newborn to intensive care unit, gradual weaning from respiratory support and correction of fluid, electrolyte and acid–base imbalance, apart from other supportive measures, e.g. antibiotics. *Blood transfusion* (O-negative, irrespective of baby's group), *10 ml/kg*, is indicated in babies with significant peripartum blood loss. *IV dopamine*, 5–10 mg/kg/min is used in shock, if blood pressure cannot be sustained with volume expanders.

When to stop resuscitation? It is a highly ethical and controversial issue though general consensus suggests futility of continued efforts in absence of heart rate for 20 minutes despite all appropriate steps in resuscitation were performed. Vigorous resuscitation is also not favored in: (a) extreme preterms <22 weeks or 500 gm, or (b) presence of lethal anomalies, e.g. anencephaly. However, decision must be individualized on contextual factors.

TABLE 12.10: Apgar scoring system

	Score		
Parameters	***0***	***1***	***2***
1. Appearance	Blue/pale	P. cyanosis	Pink
2. Heart rate	Absent	<100	>100
3. Respiration	Absent	Slow	Crying
4. Tone	Flaccid	Partial*	Flexed
5. Reflex response	Nil	Grimace	Cry

*Upper limbs flexed, lower limbs extended

Apgar score: Apgar scoring system, devised by an anaesthetist nurse Ms.Virginia Apgar, is the most popular evaluation tool to assess cardiopulmonary status at birth. Acronym APGAR stands for five evaluation parameters-***A***ppearance (color), ***P***ulse (HR), ***G***rimace (reflex response to nasal catheter), ***A***ctivity (tone) and ***R***espiration (RR).

Methodology: Apgar scoring involves assessment of these five parameters at 1 minute and 5 minute of age, on a scale of 0–2 with maximum score of 10 **(Table 12.10)**. However, if 5-minute score is <7, then additional scoring is done every 5 minutes till 20 minutes.

Utility: Apgar scoring assists to:

- Identify the need for immediate resuscitation, based on *1-minute score*.
- Predict the late neurological outcome in asphyxiated baby, based on *5-minute score*.

Limitations: the value of 1-minute Apgar score as a resuscitation guide is limited due to following reasons:

- First score is recorded at 1 minute, though resuscitative efforts should not be delayed that long.
- It is unreliable in preterms, congenital neuromuscular disorders or maternal sedation.
- Parameters, e.g. HR, tone, color and reflex activity are themselves dependent on respiration and hence, hardly provide additional information.
- Acrocyanosis (peripheral cyanosis) is common in normal newborns and hence, full score of 10 is unlikely, even in healthy crying baby.

However, 5-minutes score is an excellent predictor of late neurological outcome in asphyxiated newborns.

12.5 EXAMINATION OF A NEWBORN

Neonatal examination is difficult to complete in one sitting. A newborn has to examined repeatedly for complete evaluation, though following examinations are essential in each case: (a) preliminary examination

at birth, (b) comprehensive examination on first day in wards, (c) daily or more frequent follow-up examinations till discharge, and (d) final examination on discharge.

I. Delivery Room Examination

Delivery room examination aims to identify: (a) immediate need for resuscitation, (b) major congenital anomalies, and (c) high-risk neonate in need of advanced neonatal care and includes:

- Review of maternal and obstetrical records
- Assessment for Apgar scoring and vital signs to decide the need for resuscitation.
- Search for congenital anomalies, including orifice count and patency check if required.
- Quick physical evaluation for gestational age, birth weight and genitals for gender assignment, and
- Examination of placenta and umbilical cord for anomalies.

These aspects have been discussed in previous Ch 12.4.1.

II. First Day Examination in Nursery/Postnatal Ward

First day examination in nursery aims to evaluate the newborn *in toto*, to: (a) ensure general well-being, (b) precise assessment of gestation age, (c) identify missed congenital malformations or *warning signals* for sick newborn.

Essential prerequisites of good neonatal examination in nursery include:

- Baby should be examined at least ½ hour after feeding, when alert, comfortable and not crying.
- Nursery temperature should be comfortably warm (28–30°), and fans must be switched-off before unwrapping the baby.
- Examiner's hands should be washed properly for at least 2 minutes with an antiseptic soap and running water, dried and warmed by rubbing.
- A flexible approach is necessary in examination sequence. Traumatic examinations, e.g. patency checks or deep palpation should be deferred till inspection is complete.

A general protocol of neonatal examination in nursery includes:

I. Re-review of maternal/birth records for high-risk factors, e.g. infections, systemic illnesses, obstetric complications and drug therapy, which may affect the postnatal course of baby.

II. Anthropometry: For example, weight and length should be recorded on first day, preferably by electronic balance and infantometer respectively, while head circumference should be recorded after 24 hours, after disappearance of cranial molding.

At birth, a full term newborn weighs ~3 kg, measures ~50 cm and has a head circumference of ~33 cm. However, she/he loses up to 10% of birth weight (15% in preterms) during 1st week but regains it by 10th day (14th day in preterms). Subsequently, a newborn gain ~20–30 gm/day.

Low birth weight (<2.5 kg) or large for date (>3.5 kg) indicate specific problems in postnatal period (Ch 12.11). Birth length may be less in preterms, IUGR, chromosomal disorders and skeletal dysplasias.

III. Examination of vital signs, e.g. temperature, heart rate, respiratory rate, peripheral capillary filling and, blood pressure in selected cases.

- ***Temperature*** should be recorded by axillary digital thermometer. Normal neonatal temperature fluctuates between 36.5 and 37.4°C, with hypothermia as an important warning sign of sick newborn. WHO recommends that neonatal temperature should be recorded once a day in apparently healthy term babies, thrice a day in healthy LBW, 6-hourly in healthy VLBW < 2 kg and every 2 hourly in sick newborns. Use of mercury based rectal thermometers is no longer recommended.
- ***Heart rate*** *(HR)* in newborns fluctuates between 100 and 160/minute. Persistent tachycardia (>180) indicates CCF or arrhythmias, while bradycardia (<100) may be due to—(a) apneic episodes, (b) hypoxic-ischemic injury, and (c) maternal sedation.
- ***Respiratory rate*** (RR) in newborns is often irregular and varies from 30 to 60/minute. Common respiratory abnormalities include apnea, periodic breathing or respiratory distress.
- ***Peripheral capillary filling*** is a reliable indicator of hemodynamic status in newborns, assessed by blanching the heel and recording the time taken to recover its color. *Delayed filling of >3 second is a bad prognostic sign.*
- ***Blood pressure*** (BP) measurements are difficult and not essential in all newborns. BP may be assessed by *flush method* (Ch 17.12), though precise measurement requires Doppler studies. Normal neonatal BP is ~70–80 mm/50–60 mm Hg. While *hypotension* indicates circulatory shock, *hypertension* in newborn is usually due to: (a) renal anomalies, (b) renal artery stenosis, (c) severe coarctation of aorta, and (d) congenital adrenal hyperplasia.

IV. General physical examination needs to be more comprehensive than at-birth evaluation, conducted in a cephalocaudal direction (head-to-toe) to assess gestation age as well as identify minor/major problems, as follows:

- ***General appearance:*** A term newborn tends to assume *in utero* flexed posture and sleeps for >20 hours/day. Appearance includes: (a) posture/movements, (b) general activity, and (c) cry.

Abnormal posture: Limpness or asymmetric movements indicate—(a) hypoxic-ischemic damage, (b) CNS malformations, (c) neuromuscular disorders, (d) birth injuries or (e) pressure deformities in breech deliveries or oligohydramnios.

Abnormal activity: Persistently sluggish activity is a warning signal of sick newborn, usually due to hypoxia, sepsis, hypothermia and hypoglycemia. On the other hand, tremulousness or *jitteriness,* may indicate hypoglycemia, hypocalcemia or hypoxia.

Abnormal cry: Feeble/low-pitch cry indicates sick newborn, while high-pitch cry is common in kernicterus or hypoxic brain damage. Hoarse cry indicates birth trauma with vocal cord paralysis.

- ***Skin*** should be examined for its texture, color, vernix caseosa, lanugo, minor problems and major warning signals.

Vernix caseosa is a cheesy-white substance that covers the fetus till 34–38 weeks of gestation and the amount of vernix decreases with advancing gestation.

Lanugo are soft-fuzzy immature hair over body in preterms, which are gradually replaced by mature vellus hair with advancing gestation.

Skin in term newborn is shiny, pink, with vernix present only at creases and lanugo present only at upper back and dorsum of limbs.

Skin in preterms is thin and delicate, bright-red color, with plenty of vernix and lanugo over entire body. Pedal edema is also common.

Skin in post-terms is lusterless that peels or cracks at creases, and may be yellowish due to intrauterine passage of meconium.

Common benign skin abnormalities in newborns are discussed in Ch 12.7.

Important ***warning signals*** on skin include: (a) severe pallor/plethora, (b) persistent/central cyanosis, (c) deep icterus, (d) *cutis marmoratus*, i.e. pale-mottled skin suggestive of sepsis or hypothermia, (e) bleeding spots, e.g. petechiae or ecchymosis, due to birth injury or bleeding disorders, (f) *sclerema*, i.e. diffuse hardening of skin over cheeks, buttocks, extremities and bony prominences seen in hypothermia, sepsis and hypoglycemia, (g) generalized edema, e.g. hydrops fetalis, and (h) severe infections.

- ***Head*** must be examined for—(a) shape, (b) circumference, (c) soft-tissue abnormalities, and (d) fontanels and sutures.

Shape may be transiently deformed at birth, due to *molding*—overriding of cranial bones by vaginal pressure, which gradually disappears in a few days. *Excessive molding* indicates obstructed/prolonged vaginal delivery.

Head circumference of a normal newborn is ~33–35 cm, which should be recorded only after 24 hours of birth, after molding disappears. *Small size* indicates microcephaly or craniosynostosis, while *macrocephaly* may be familial or due to CNS malformations, e.g. congenital hydrocephalus, hydroencephaly, etc.

Soft-tissue abnormalities of scalp are usually benign, e.g. caput succedaneum or cephalohematoma (Ch 12.10.2). *Craniotabes*, i.e. ping-pong feel due to compressible skull-vault, is physiological in newborns. Large caput, cephalohematoma or lacerations over scalp may indicate significant birth injury.

Anterior fontanel at birth is open, soft, flat and pulsatile with diagonal size of <3 cm, while *posterior fontanel* is closed or admits only a tip of finger. Cranial sutures are open but in close approximation. *Large fontanels* or wide-sutures at birth indicate: (a) prematurity, (b) hydrocephalus, (c) hypothyroidism, (d) osteogenesis imperfecta, etc. *Small fontanels suggest* microcephaly/craniosynostosis. A *third fontanel* between anterior and posterior fontanel, is not a true fontanel but a defect in parietal bones, occasionally present in normal newborns or Down syndrome.

- ***Face*** should be examined for dysmorphic features and asymmetry during cry.

Facial dysmorphism is an important indicator of chromosomal or genetic disorders and generally includes—low hair-line, low-set ears, pre-auricular tags, slanting eyes, epicanthic folds, hyper/hypo-telorism, depressed nasal bridge, micro/retrognathia, cleft lip, etc.

Facial asymmetry on crying may be due to congenital hypoplasia of depressor angularis oris muscle or birth injuries (facial palsy, mandibular injury).

- ***Eye*** examination is difficult in newborns due to *physiological photophobia,* though most babies may open eyes on gentle rocking. A quiet and alert newborn may fix the vision on examiner's face and follow it for few degrees of sideway movements. Pupillary reflex is present from 28th week of gestation.

Common eye abnormalities include: (a) *benign problems*, e.g. conjunctival hemorrhage, nasolacrimal duct obstruction, transient discharge, etc.; (b) *malformations* suggestive of intrauterine infections or chromosomal disorders, e.g. microphthalmia, micro/macrocornea, coloboma, cataracts, or cat-eye-reflex, etc.; and (c) *conjunctivitis*.

- ***Ears*** should be examined for—(a) shape, recoil and deformities, (b) otoscopic exam in select cases and (c) hearing by startle response to sudden sound. Term newborns have well-formed cartilaginous pinna with good elastic recoil, relatively short and straight external auditory canal, easily visible dull-grey tympanic membrane and good startle response.

Transient ear discharge is common during first few days due to retained amniotic fluid. In preterms, ear cartilage is under-developed with slow recoil. Important ear abnormalities include malformed/low-set ears (chromosomal disorders), pre-auricular pits/tags (associated renal anomalies) and persistent discharge (otitis media), etc.

- ***Nose*** should be examined for dysmorphism and patency (by lubricated soft-rubber catheter, if required). Most newborns are obligate nose-breathers.

  Common abnormalities include depressed nasal bridge (hereditary, chromosomal), and *stuffiness* (choanal atresia/stenosis, infection, postural, etc.)
- ***Oral cavity*** must be inspected for cleft lip/palate or benign problems, e.g. natal tooth.
- ***Neck*** is relatively short in newborns but with full movements. Neck injuries are common in breech/transverse lie and may lead to torticollis or sternocleidomastoid tumor (Ch 12.10.2).

  Important neck abnormalities include *webbing* (Turner syndrome), *mid-line mass*, e.g. goiter, cystic hygroma, thyroglossal cysts, and *lateralized lesions*, e.g. branchial cysts/sinuses.
- ***Chest*** must be examined for shape, size, breast nodules, rib-cage and respiratory movements. Neonatal chest is barrel-shaped with prominent xiphisternum. Chest circumference is lesser than head circumference at birth. Breast nodule is ~10 mm in fullterms, with well-defined areola.

  Apart from benign problems, e.g. supernumerary nipples and mastitis neonatorum, also look for wide-spaced nipples (Turner syndrome), tender rib-cage (birth injury) and increased intercostal movements suggestive of respiratory distress.
- ***Spine*** in newborns is relatively straight and more flexible, which should be examined for neural tube defects or its stigmata (midline dimple/tuft of hair, etc.). Sacrococcygeal teratoma presents as a mid-line sacral tumor over spine at birth.
- ***Limbs*** abnormalities may be due to fetal posture, birth injury or congenital malformations. Sole creases are present up to anterior 2/3rd or more of sole in fullterms.

  Common limb problems include—(a) *congenital defects*, e.g. poly/syndactyly, hip dislocation, clubfoot, amniotic bands, etc., (b) *traumatic lesions,* e.g. fractures *or* brachial plexus injuries. Abnormal dermatoglyphics, e.g. simian crease, may indicate chromosomal defects.

  All newborns, specially with breech delivery or oligohydramnios, must be screened for congenital dislocation of hip by Ortolani/Barlow test (Ch 23.2.2).
- ***External genitals*** must be examined to assess gestation and exclude ambiguous genitalia.

  A fullterm male newborn has stretched penile length of 3–4 cm, less-retractile prepuce (physiological phimosis), pigmented scrotum with extensive rugae, and well-descended testes. Penile erection is common.

  Important male genital problems are—micropenis (<2.5 cm at birth); epi/hypospadias; hyperpigmented scrotum in congenital adrenal hyperplasia; undescended testes, hydrocele and inguinal hernia. Testicular volume is unusually small in Noonan syndrome and Klinefelter syndrome and unusually large in Fragile-X syndrome.

  Term female newborns have well-developed labia majora that cover > 2/3rd of minora. A non-purulent discharge is common during 2–7th day due to transplacentally transferred maternal hormones. Some babies develop transient vaginal bleeding on 5–7th day, due to estrogen-withdrawal.

  Common and usually benign female genital abnormalities include labial adhesions, imperforate hymen, hymenal tags and clitoral hypertrophy, though last may be a sign of adrenogenital syndrome. Urine is passed with 24 hours by >95% newborns, *else* should alert about possibility of obstructive uropathy, e.g. posterior urethral valves in males or dehydration.
- ***Anus*** examination is essential in cases who have not passed meconium for 48 hours and includes visual inspection. Also look for fistulous outlets.

V. Umbilical examination is an essential part of neonatal assessment, being the commonest portal of entry for infections.

Normal umbilical cord is ~30–50 cm in length and contains two arteries, one vein, remnants of omphalomesenteric (vitalline) duct, rudimentary allantois and a gelatinous substance (*Wharton's jelly*), all covered by amniotic sheath. Post-delivery, the umbilical stump dries-up and shrivels within 24 hours to turn yellowish black and fall-off by 7–8th day. Umbilical arteries constrict at birth or within 4–6 hours, while vein may be cannulated till 5–7th day. Later, umbilical arteries and vein form *lateral umbilical ligaments* and *ligamentum teres*, respectively.

Common umbilical anomalies at birth include:

- *Single umbilical artery* is present in 5–10/1000 singleton and 35–70/1000 of twin births and signifies presence of other congenital anomalies in ~ 1/3rd cases.
- *Delayed separation of cord* stump beyond >10th day indicates umbilical sepsis or defects of phagocytic function; while *early separation* is usually traumatic (avulsion injury).
- *Umbilical bleeding* may be due to—(a) slipped ligature, (b) trauma, (c) sepsis, or (d) systemic bleeding disorders.
- *Umbilical discharge* is usually due to—(a) sepsis (purulent); but rarely may indicate, (b) patent omphalointestinal duct (fecal discharge), or (c) patent urachus (urinary discharge).
- *Omphalocele*, i.e. herniation of abdominal contents through umbilical ring, covered only by peritoneum without overlying skin (d/d umbilical hernia) may be an isolated defect *or* seen in Trisomy 13 or Beckwith's syndrome. As the herniated sac may contain vital structures, e.g. intestines or liver, it should be immediately covered with sterile saline gauze to prevent drying, till surgery is arranged.
- *Umbilical sepsis, see* Ch12.15.1.

VI. Abdominal examination includes inspection for abnormal appearance or distension (record girth, if distended) as well as palpation for liver, spleen, kidney or unusual mass. At birth, liver may be palpable up to 2 cm, as also the splenic tip and lower poles of kidneys.

Common abnormalities in appearance include: (a) *scaphoid* abdomen in congenital diaphragmatic hernia, (b) *distended* abdomen in necrotizing enterocolitis, intestinal, obstruction or paralytic ileus, and (c) *parietal wall defects*, e.g. omphalocele, ectopia vesicae, gastroschisis, or *prune-belly syndrome*

Hepatosplenomegaly at birth usually indicates intrauterine infection. Ascites in newborns indicates: (i) hydrops fetalis, (ii) lymphatic malformations, or (iii) severe renal disease.

VII. Respiratory examination aims to assess the presence, severity and etiology of respiratory distress (Ch 12.13). Auscultatory findings are unreliable in newborns and should be supported by X-ray, if necessary.

Excessive oral frothing *or* gurgling sounds on chest auscultation, are warning signs for *tracheo-esophageal fistula* and *diaphragmatic hernia,* respectively.

VIII. Cardiovascular examination aims to assess: (a) location of heart sounds, as well as (b) presence of murmurs.

Presence of better audible heart sounds in right hemithorax indicate dextrocardia, situs inversus or dextroversion (due to right lung aplasia or left pneumothorax). In newborns, splitting of S_2 is easily audible with loud P_2 due to high pulmonary vascular resistance.

Presence of a murmur in newborn not necessarily indicates congenital heart disease, since transient functional murmurs are present in 15–20%. Conversely, the absence of murmurs does not exclude a heart disease, as many lesions manifest later when pulmonary vascular resistance drops after lung expansion.

IX. Neurological examination on first day includes assessment of—(a) general behavior, e.g. alertness, activity and cry, (b) active/passive tone, (c) symmetry of limb movements, and (d) primitive neonatal reflexes. Newborn should be neurological examined only when quiet but alert—*Prechtl stage III* **(Table 12.11)**, usually after 1 hour of feeds.

- *Abnormal behavior*, e.g. staring spells, vacant look or shrill cry may indicate seizure activity in newborns, while sluggish activity is a warning sign for septicemia, hypothermia, hypoglycemia and asphyxia. *Jitteriness* indicates hypoglycemia or hypoxic brain injury.
- *Tone* may be assessed indirectly by posture (flexed/extended) or directly by various methods for active tone (arm recoil) /passive tone (Popliteal angle, scarf sign, Heel-to-ear maneuvers) (Ch 12.10.1). *Hypotonia* at birth is a sign of prematurity, neuromuscular disorders, birth asphyxia or critical illnesses, while *Hypertonia* indicates kernicterus, tetanus neonatorum or cerebral damage.
- *Asymmetric limb movements* may be due to *true weakness*, e.g. brachial plexus injury, neural tube defects, etc. *or pseudo-paralysis* in local painful conditions, e.g. fractures, septic arthritis, congenital syphilis, etc.
- *Primitive neonatal reflexes* (NNR) are excellent indicators of neurological disease (*see* below). *Absent or sluggish NNRs* usually indicate prematurity, critically sick newborn or sedation.
- *Deep tendon reflexes* may be exaggerated in newborns due to immature myelination and *ankle clonus* is common. Asymmetry of these reflexes is more informative, suggestive of neuromuscular disorders.
- *Plantar response* is normally extensor in newborns, with a little clinical significance.

Primitive neonatal reflexes, which appear and disappear in fairly consistent sequence during specific periods of development **(Table 12.12, Fig. 12.5)** are excellent indicators of neonatal health, neurological status and development. Note that:

- While most NNRs start developing in late gestation, they mature gradually to reach the optimal level only in full terms. Hence, the strength of reflex response is as important as its presence.
- Absent/sluggish NNRs, apart from illness, may also be due to physiological factors, e.g. feeding or sleep.
- Disappearance of a NNR is necessary before reaching the corresponding milestone, e.g. tonic neck reflex disappears before crawling.
- Persistence of NNRs, beyond the expected age is an important indicator of cerebral palsy.

TABLE 12.11: Prechtl stages of neonatal behavior

Stage	*Behavior*
I	Quiet non-REM sleep, regular breathing
II	REM sleep, irregular breathing
III	*Quiet awake:* Eyes open, minor movements
IV	Active, alert, moderate movements
V	Crying

REM: Rapid eye movement

TABLE 12.12: Common primitive neonatal reflexes

NNR	*Appears*	*Disappears*
Moro's*	28–32 weeks	3–4 months
Sucking/rooting	32–36 weeks	4–6 months
Palmar grasp	28–32 weeks	3–4 months
Plantar grasp	32–36 weeks	8–10 months
Stepping	32–36 weeks	3–4 months
Crossed extension	32–36 weeks	4–6 months
Landau	32–36 weeks	24 months
Tonic neck reflex	1–2 months	4–6 months
Parachute	6–8 months	Persists

*Moro's is the first reflex to appear and disappear

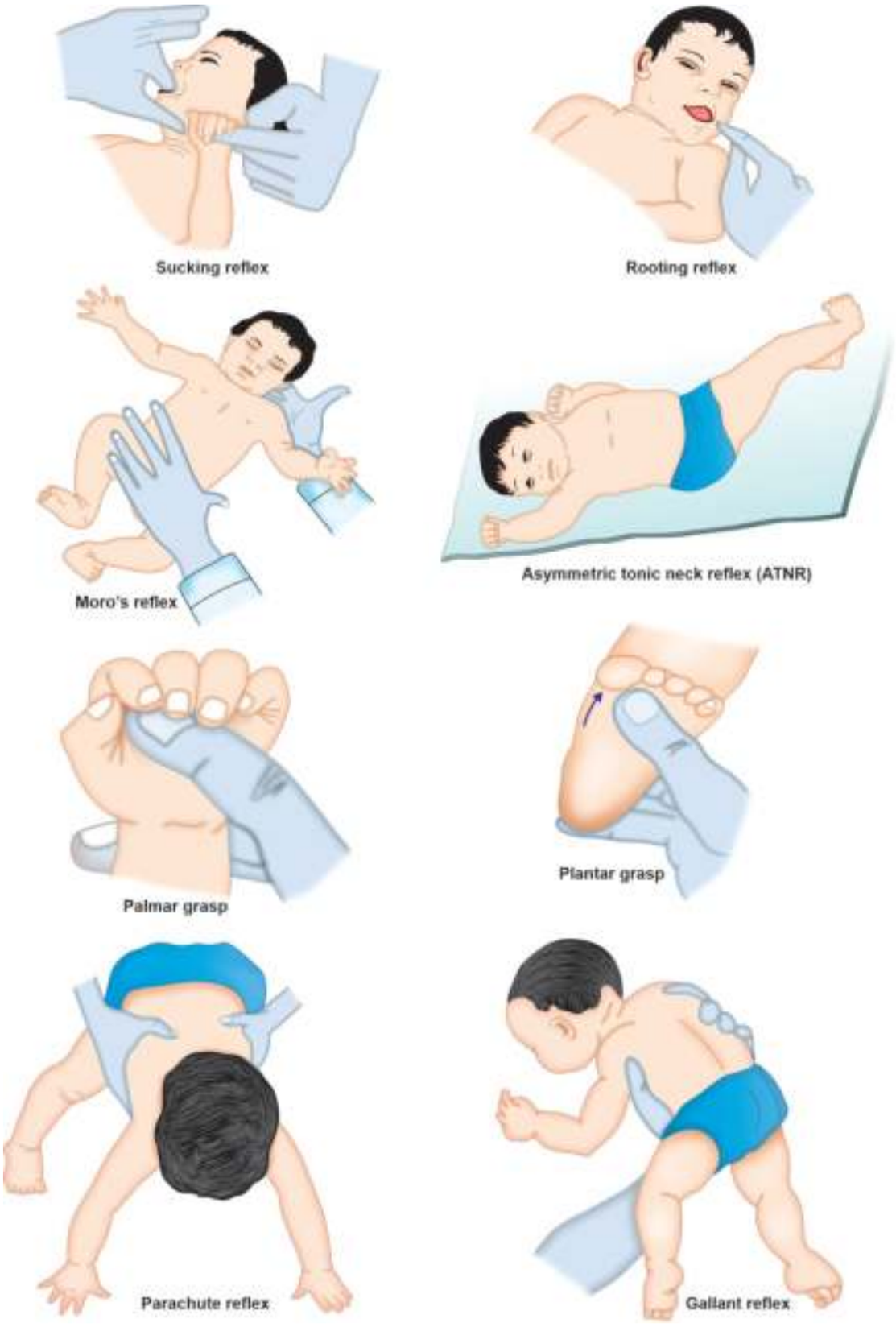


Fig. 12.5: **Common primitive neonatal reflexes.**

Common primitive NNRs are as follows:

Sucking reflex is elicited by touching the baby's lips with a clean finger, leading to sucking movements that should be assessed for strength and rhythm. It is present but weak at 28th week but strong enough by 32 weeks.

Rooting reflex is elicited by stimulating the baby's lips or corner of mouth by examiner's finger, leading to movement of lips/tongue and turning of the head towards the same side, as in search of breast. Sucking and rooting reflexes together are also called *cardinal point reflexes.*

Moro's reflex is elicited by pulling the supine baby halfway to sitting position and suddenly letting his head fall back a short way, supported by examiner's hand. The response consists of sudden abduction and extension of arms with opening of fists (Phase I), followed by adduction and flexion in arms-embracing position (Phase II). Asymmetric Moro's reflex indicates brachial plexus injury or fracture of clavicle.

Startle reflex, elicited by sudden noise (clapping of hands) is similar to Moro's reflex, except flexion rather than extension of arms and absence of second component. Sluggish startle response indicates hearing impairment.

Palmar grasp reflex is elicited by stroking the baby's palm with examiner's index finger, leading to flexion of fingers to grasp it, which is reinforced on attempts to remove the finger. In fullterms, grasp may be strong enough to support the baby's weight. Grasp reflex has to disappear, before the baby learns to release the objects. Persistent grasp is a reliable indicator of cerebral palsy.

Plantar grasp reflex is elicited by stroking the anterior 1/3rd of sole, leading to flexion of toes. Plantar grasp disappears before baby learns to walk.

Stepping reflex (*limb-placement reflex*) is elicited by rubbing the shin of tibia on the side of table that leads to lifting of leg over table's edge.

Walking reflex is elicited by holding the baby upright and pressing the sole of one foot on couch, leading to flexion of opposite leg, as in walking.

Asymmetrical tonic neck reflex (ATNR) is elicited by turning the baby's head to one side, leading to extension of ipsilateral arm and flexion of contralateral knee (*Fencer's position*). ATNR has to disappear before the baby learns to turn from supine to prone position.

Symmetric tonic neck reflex is characterized by extension of arms and flexion of knees when the head is flexed and vice versa. This reflex has to disappear before the baby starts crawling.

Crossed-extension reflex is elicited by gently stroking the sole of a leg *held in extension*, leading to rapid flexion, adduction and then extension of opposite leg. Although this reflex appears at 32 weeks, adduction component is absent in preterms.

Parachute reflex is a protective reflex that appears before walking starts, elicited by holding the baby in ventral suspension and suddenly dropping to some distance, leading to extension of arms, hands and fingers. It is absent or asymmetric in cerebral palsy.

Landau reflex is elicited by holding the baby in ventral suspension, leading to extension of head, spine and legs. Flexion of head in this position leads to flexion of limbs.

III. Subsequent Examinations Till Discharge

Neonatal examination is never complete in one sitting. During hospital stay, all babies need to be re-examined at least twice a day for any warning sign (*see* **Table 12.14)**. However, baby must not be handled too frequently to avoid infections. Routine evaluation on ward rounds include:

- ***History*** regarding—(a) acceptance of feeds, (b) passage of meconium/urine, and (c) other significant events. Failure to pass urine till 24 hours and meconium till 48 hours indicates need of detailed evaluation.
- ***General examination*** specially for—(a) behavior, activity and cry, (b) vital parameters, (c) weight record, (d) icterus, (e) umbilical sepsis, (e) superficial infections, e.g. thrush, conjunctivitis, pyoderma, rash, etc., and (g) warning/danger signs.
- ***Systemic examination*** specially for—(a) abdominal distension, (b) new murmurs, and (c) NNRs.
- ***Maternal examination*** for—(a) general health and diet, (b) local breast/nipple problems, and (c) counseling regarding breastfeeding, temperature control and good baby care practices.

IV. Examination at Discharge

A normal newborn may be discharged after 48 hours, though preterms/small for date and sick newborns need to stay longer. Examination at the time of discharge aims to ensure eventless course at home and includes:

- Thorough clinical examination to exclude danger signals and hitherto missed congenital anomalies.
- Proper maternal counseling about feeding, thermocare, immunization, follow-up, birth registration, and further family planning.

12.6 CARE OF NORMAL NEWBORN

Care of a normal newborn in delivery room has already been discussed earlier. This chapter deals with care in postnatal wards/home.

- **'Rooming in',** i.e. keeping the baby with mother is best option for normal newborns to facilitate—(a) emotional infant–mother bonding, (b) successful lactation, (c) maternal involvement in baby care and (d) prevention of nosocomial infections.
- **Thermoregulation:** Hypothermia is a leading cause of morbidity in normal newborns, which may be prevented by—(a) proper room temperature

(~ 28–30°C), (b) avoidance of direct wind movements, e.g. fans, (c) proper cloths* and wrapping of baby in clean sheets and caps, (d) delayed bath till next day, and (e) oil application without vigorous massage to provide protective insulation against insensible heat loss and stimulation to baby (*touch therapy*).

*Two layers (inner vest and outer frock, to trap the warmth) of soft, loose, easy to wear cotton clothes are advised with additional layers of soft woolen including cap and socks in winter season. Synthetic clothes and diapers must be avoided. A square piece of cotton may be used as diaper.

Kangaroo care is an excellent method to prevent hypothermia, specially in preterms/low birth weights, which involves placement of baby inside mother's clothing with close skin-to skin contact (*see* **Fig. 12.12)**. It also stimulates lactation and emotional bonding between mother and baby.

- **Feeding:** Breastfeeding should be initiated as early as possible, preferably in the labor room itself. Successful lactation requires—(a) early initiation, (b) constant motivation, (c) conductive atmosphere, e.g. privacy, (d) demand feeding, (e) no pre-lacteal feeds, (e) proper technique, (g) management of breast/nipple problems, and (h) adequate maternal nutrition (extra 400–500 calories).
- **Care of the skin:** At birth, baby is covered with vernix caseosa and amniotic fluid, which should be gently wiped-off in delivery room, though vigorously scrubbing should be avoided. The need for first-day bath is controversial and should be avoided during winter season. Subsequently, baby may be bathed or sponged next day with lukewarm water and unmedicated soap. Medicated, e.g. chlorhexidine soap are not advisable, which may be irritant to tender skin and prevent colonization with normal flora. *Dip-baths* should be avoided till cord has fallen.

  Pre-bath gentle oil massage with a non-irritating oil, e.g. olive or coconut oil, is claimed to comfort the baby, improve muscle tone, and strengthen maternal bonding (***touch therapy***). However, due care is necessary to prevent trauma and hypothermia. Practice of instilling a few drops of oil in nose and ears, prevalent in some communities, may lead to aspiration and should be strongly discouraged.
- **Care of umbilical stump:** Umbilical sepsis is the commonest source of infection in normal newborns. It should be kept dry, clean and unsoiled from urine/stool. No topical antibiotic or antiseptic application is required. Cord stump usually falls off on 7–10th day, unless infected. Cord should be regularly examined for signs of umbilical sepsis, e.g. foul smelling pus discharge and peri-umbilical induration.
- **Care of eyes:** Sticky eyes are common in newborns and not necessarily indicate infection. Excessive watering or stickyness may be due to nasolacrimal duct blockage, which opens up spontaneously after 3–6 months. Eyes say be cleaned at birth and then periodically with a sterile cotton-swab soaked in normal saline.
- **Medications** are rarely needed, except:
  - *Single dose of vitamin K* (0.5–1.0 mg, PO/IM) to all normal newborns at birth. Low birth weight or sick newborns should receive it by IM route only.
  - *BCG, OPV and HBV* vaccine is indicated to all newborns before discharge.
  - *IV tetanus immunoglobulin* 250–750 IU, only if mother had not received TT in antenatal period and delivered by untrained *dai*/cord cut by unsterile blade.
- **Clinical monitoring** for—(a) weight changes, (b) warning signals (*see* **Table 12.17)** and (c) adequacy/problems related to breastfeeding. Cases with warning signals need transfer to intensive care.
- **Maternal/family counseling** regarding essential aspects of child care, e.g. prevention of hypothermia, breastfeeding, maintenance of hygiene, etc. should be reinforced on daily rounds and on discharge.

When to discharge: A normal newborn may be discharged after 24 hours, if—(a) accepting feeds properly, (b) has passed urine and stools, (c) has no warning signs as in **Table 12.17**; (d) has received at-birth immunizations, and (e) mother has been counselled about routine newborn care and recognition of warning signs. Follow-up is indicated at 6 weeks.

Follow-up care: *Indian Academy of Pediatrics (IAP)* recommends periodic growth assessment of newborns and infants at—(a) birth, (b) during each immunization visits at 6,10,14 weeks and 6, 9 and 15 months, (c) every 6 months from 18 months to 8 years of age and then, (d) annually during 9–18 years.

During each of these visits, baby should be assessed for—(a) growth, (b) immunization status, (c) common health problems, (d) specific health concerns reported by parents. In addition, mother should also be counseled about infant feeding practices, immunization needs, importance of growth monitoring and watch for red-flags signs.

12.7 MINOR PROBLEMS IN NEWBORNS

Although essentially benign and frequently self-limiting, following problems are common cause of parental concern. No treatment is indicated in these cases, except assurance. However, some of them must be differentiated from more serious pathologies, discussed in later chapters.

a. Common skin problems include:

Milia, i.e. tiny, white dots over nose and face due to blocked and distended sebaceous gland, are common on 2–3rd days and disappear spontaneously **(Fig. 12.6)**.

TABLE 12.13: Common rashes in newborn

Benign and transient
- Milia
- Erythema toxicum
- Pustular melanosis

Pathological
- Staphylococcal pustules,
- Intrauterine infections, e.g. HSV, syphilis
- Cutaneous thrush (candidiasis)
- Staphylococcal scalded skin syndrome
- Toxic epidermal necrolysis

Erythema toxicum, i.e. tiny, discrete, erythematous papules/vesicles over face, trunk and extremities, usually appear on 1–3rd day and persist for as long as one week, before spontaneous resolution **(Fig. 12.6)**. On scrapping, these lesions are filled with eosinophils.

Pustular melanosis *are* benign vesiculobullous eruptions over chin, neck, back and limbs, present at birth, lasting for 2–3 days **(Fig. 12.6)**. On scrapping, these lesions are filled with neutrophils. (***d/d*** Impetigo or Herpes simplex). Some common causes of neonatal rash are given in **Table 12.13**.

Mongolian spots, i.e. slate-blue, well-demarcated spots on trunk, back or buttocks, are present in >50% newborns and usually disappear by 6–24 months **(Fig. 12.6)**. These spots have no relation with Down syndrome. (*d/d Congenital melanocytic nevi*, seen in <1% newborns).

Stork-bites (Salmon patch), i.e. small, diffuse, pinkish-grey macules (capillary hemangioma), are seen in ~40% newborns, specially over eyelids, forehead and nape of the neck (*see* **Fig. 25.3)**. These lesions are usually bilateral, symmetrical and more prominent during cry. Most of them fade spontaneously in 1–2 months. (*d/d Port wine stains*, present at birth as flat, circumscribed, unilateral macules in head/neck region, which enlarge and darken with age).

Acrocyanosis over finger tips and perioral region is very common during first few days of life, which becomes more prominent during cry and improves rapidly after protective clothing. (*d/d* central or persistent cyanosis in cardiorespiratory disorders).

Harlequin color change, i.e. a transient vertical delineation of body into red and pale halves, is a striking but harmless sign of vasomotor instability in first few day of life. (*d/d cutis marmorata*-bilateral diffuse mottling with lacy appearance, suggestive of sepsis or hypothermia).

Physiological jaundice appears in ~70–80% of normal newborns on 2–3rd day of life, and persists till 7–10th day in terms and 10–14th day preterms (*d/d see* Ch 12.14.1).

Edema: Transient pedal edema is common in preterms, while its persistence indicates possibility of Turner syndrome or lymphatic malformations, e.g. Milroy disease. (*d/d* generalised edema is seen in hydrops *fetalis,*

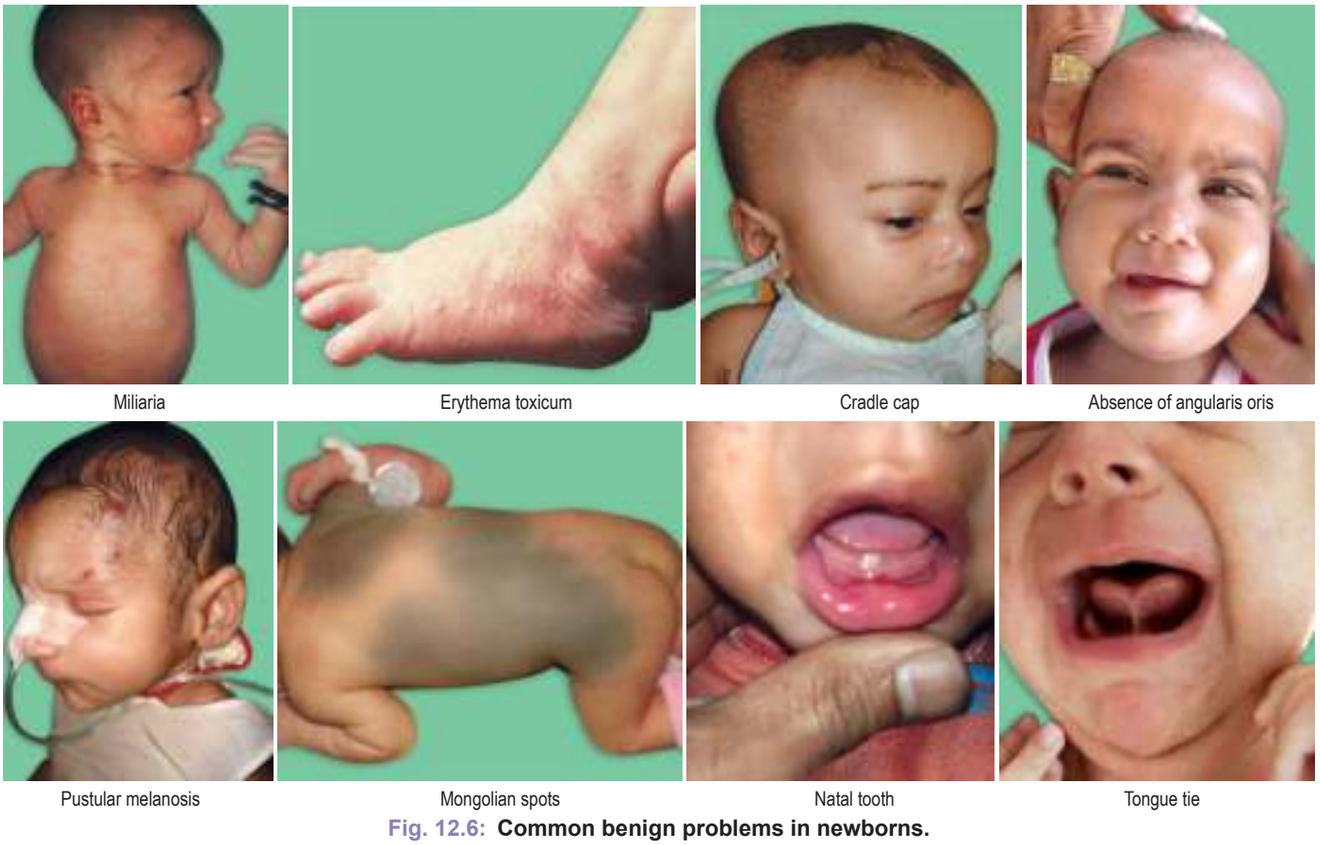


Fig. 12.6: Common benign problems in newborns.

of immune (Rh-incompatibility) or non-immune (renal agenesis, severe anemia) origin.

Subcutaneous fat necrosis, i.e. patchy induration over buttocks, cheeks and limbs that resolves spontaneously. (*d/d* diffuse *sclerema* in sepsis, hypothermia).

b. Common problems of oral cavity include:

Epstein pearls are tiny, white masses over hard palate near midline, due to temporary accumulation of epithelial cells (retention cysts) that disappear spontaneously within a few weeks. Similar lesions may be present on gums (epithelial pearls) and prepuce (prepucial pearls).

Sucking pads/sucking callus are temporary callosities over lips and cheeks respectively, due to accumulation of extra fat and stratified epithelium, which disappear after some time.

Natal tooth are not uncommon in normal newborns, usually seen at the site of lower incisors, representing a supernumerary or prematurely erupted deciduous tooth **(Fig. 12.6)**. Extraction is not indicated unless loose or hurts during breastfeeding. (*d/d* Ellis-van Creveld syndrome).

Tongue-tie due to short ventral frenulum is common, but rarely leads to feeding or speech problems **(Fig. 12.6)**. A thick and tight frenulum with notches over the tongue, may be snipped at 3 months.

c. Common ocular problems include:

Physiological photophobia is common in normal newborns during first few weeks of life.

Subconjunctival hemorrhage, usually near the outer canthus is common in vertex delivered newborns, which resolve spontaneously in 1–2 weeks.

Unilateral mucoid eye discharge is seen in ~5% of newborns, due to incomplete canalization of naso-lacrimal duct. Frequent massage over nasal sides and cleaning of eyelids with lukewarm water is enough in most cases, before spontaneous resolution by 3–6 months. Topical antibiotics are indicated only if discharge is mucopurulent. Persistent cases (>6 months) may need punctal probing or dacryocystorhinostomy.

d. Common genital problems include:

Physiological phimosis is present in ~80% newborns, which rarely interfere with micturation and resolves spontaneously by 2–3 years. *Prepuce should not be etracted forcibly*.

Transitory hydrocele due to persistent *processus vaginalis* is common in male newborns, presenting as unilateral scrotal enlargement with small fluid-sac and usually resolves spontaneously by 3–4 months.

Vaginal discharge: A whitish, mucoid vaginal discharge is common in female babies during first few days of life, due to the transplacentally transferred maternal estrogen on vaginal mucosa. No treatment is required. (*d/d* purulent discharge in infections).

Vaginal bleeding: 20–25% female babies develop vaginal bleed on 3–7th day due to withdrawal of maternal estrogens. It clears spontaneously in 2–3 days, with no specific treatment except local cleaning. (*d/d* hemorrhagic disease of newborn or other bleeding disorders).

e. Mastitis neonatorum is a misnomer, since it is not an infection but merely indicates breast hypertrophy on 3rd–4th day, due to effects of transplacental maternal hormones and disappears in a few days. A creamy liquid may also ooze-out from nipples. No treatment is necessary. Engorged breast should not be squeezed, which may cause inflammation.

f. Common GIT problems include:

Vomiting: Transient vomiting soon after birth may be due to swallowed maternal blood/amniotic fluid, which may be easily controlled by gastric lavage.

Possetting, i.e. effortless regurgitation of some curdy milk is common in newborns and indicates developmental immaturity of cardiac sphincter in early infancy. It is more common in vigorous babies, during rapid limb movements and soon after feeding.

Aerophagia, i.e. swallowing of air during feeding and overfeeding are two commonest causes of possetting, specially in bottle-fed babies. Adequate burping after each feed is all that is required in these cases. Vomiting associated with bile, blood, abdominal distension or poor weight gain in newborn is pathological and need detailed evaluation.

Diarrhea: Appearance and frequency of stools in normal newborns vary according to the postnatal age and type of feeding, apart from individual variations.

- ***Meconium,*** *the Initial stools* during first 48–72 hours are typically black, thick, viscid and odorless, passed 5–6 times a day. The color and consistency changes gradually to transitional stools.
- ***Transitional stools,*** from 3–7th day are relatively watery, greenish, explosive and contain mucus or solid soapy flakes. Stools may be passed ~8–10 times/day, gradually culminating into breast-milk or top-milk stools.
- ***Breast-milk stools:*** A breastfed baby passes dark yellow or greenish semi-watery stools, usually 5–6 times a day but frequency may vary from once a week to 10–15 times a day. Although worrisome for parents, this pattern is physiological and must not be construed as diarrhea.
- ***Top-fed babies*** tend to be relatively constipated and pass thicker and lighter stools.
- ***Hyperactive gastro-colic reflex*** is a common cause of increased stool frequency in newborns and early infancy, characterized by passage of stools soon after feeding. Problem improves spontaneously by 3–6 months.

Pathological diarrhea is more common in top-fed or sick newborns, indicated by sudden increase in frequency and fluidity of stools and needs need careful evaluation.

Constipation: Nearly 95% of newborns pass first stools within 24 hours of birth, and failure to do so by 48 hours indicates possibility of intestinal obstruction or ano-rectal malformations. Newborns with higher intestinal atresia, e.g. duodenal atresia, may pass 1–2 stools initially, before developing absolute constipation and abdominal distension.

Constipation is a common cause of parental concern, though normal variations are common in stool frequency. Top-fed children tend to be more constipated due to high-solute load and relative dehydration. Mild constipation may be overlooked, though significant discomfort may be relieved by glycerine rectal suppository after excluding pathological causes.

Constipation from 2nd week of life, with/without intermittent attacks of diarrhea suggests a possibility of Hirschsprung disease or hypothyroidism.

Hiccups: Most normal newborns develop hiccups, specially after feeds, due to distension of stomach with diaphragmatic irritation.

g. Dehydration fever: Some healthy newborns may develop transient fever on 2–3rd day of life, specially during summer season due to immature heat-loss mechanisms. Fever rarely exceeds 38.5°C and baby remains active and keen to feed. No treatment is required except adequate feeding and reducing the environmental temperature.

h. Sneezing or noisy breathing is common in newborns, frequently confused with *common cold*. As newborns are obligate nose-breathers, severe nose block may interfere with feeding, which can be managed with nasal instillation of 1–2 drops normal saline, 10–15 minutes before feeds. Nasal decongestants are contraindicated.

i. Excessive cry: During first 4–6 weeks, babies usually sleep throughout the day and cry at night probably due to *in utero* pattern. (*in utero* babies sleep while pregnant mother is working in daytime due to rocking effect).

While duration, intensity and pattern of cry may vary in different newborns, common causes may be—(a) hunger, (b) discomfort, e.g. wet, soiled, too hot, too cold, (c) insect-bites, (d) aerophagia or abdominal colic (e) blocked nose, and even (g) loneliness.

Babies often cry before passing urine due to unpleasant sensation of full bladder. However, crying during (rather than before) micturation may indicate dysuria with possibility of urinary tract infection.

Some unusual neonatal cries include *shrill high-pitched* cry in kernicterus or cerebral hypoxia; *weak, low-pitched* cry in hypotonia disorders; *intermittent* cry in abdominal colic, *sudden cry* due to insect-bite, etc.

Evening colic is well-recognized entity of unknown etiology, characterized by unexplained sudden crying spells during evenings with flexion of thighs and flushing of face. Each spell lasts for a few minutes to a few hours and continues for many days with consistent regularity and timing before spontaneous disappearance by 2–3 months (Ch.4.1).

12.8 HIGH-RISK NEWBORN

High-risk newborn is defined as "*a newborn with abnormal maternal, antenatal, peripartum or neonatal indicators, suggestive of higher than the normal risk of morbidity and mortality, who should be under close observation by experienced pediatrician and nurses*".

About 10% of all live births fall in this category, which need to be either delivered in a hospital set-up or immediately transferred to intensive care unit.

Indicators: A high-risk newborn may be identified at birth due to: (a) high-risk pregnancy, (b) high-risk delivery or (c) postnatal characteristics, e.g. abnormal gestation, birth weight, congenital malformation, etc. Other newborns are added to this category, when exhibit any *warning signals* in later neonatal period **(Table 12.14)**.

Care of a high-risk newborn depends on the time when the risk is identified and the expected severity of complications. While specific measures are discussed in later chapters, important management strategies include:

- Early identification of high-risk pregnancy during antenatal visits, referral to a suitable neonatal care center and if possible, intrauterine interventions.
- Comprehensive review of case-records before delivery for resuscitation alert and adequate resuscitation facility/expertise at the time of delivery.
- Assessment of delivered newborn for high-risk status or warning signals and timely transfer to appropriate neonatal care center.

TABLE 12.14: High-risk neonate

- **History of high-risk pregnancy (Table 12.2)**
- **History of high-risk delivery (Table 12.7)**
- **High-risk neonatal factors at birth**
  - Prematurity/postmaturity
  - Small for date/large for date
  - Major congenital malformations
- **Presence of warning (Danger) signals**
  - Sluggish activity or cry
  - Inability/refusal to accept feeds
  - Hypo/hyperthermia
  - Respiratory distress
  - Vacant stare, seizures or jitteriness
  - Not passed urine within 24 hours
  - Not passed meconium within 48 hours
  - Appearance of icterus <24 hours
  - Persistent vomiting, choking or frothing
  - Abnormal bleeding

Levels of neonatal care: According to the facilities and expertise, neonatal care centers are classified into three levels (*tiers*):

Level I care is the minimal care level, that should be available to all normal term newborns with birth weight *>2000 gm.* It may be provided at home or peripheral health center with minimum facilities and includes:

- *Basic antenatal care*, including identification of high-risk pregnancies.
- *Delivery*, by traditional birth attendant, using safe delivery practices. *Basic delivery kit*, supplied to these workers under MCH programs include—a sterile blade, clean thread, cotton gauze and an antiseptic soap.
- *Essential neonatal care* including—(a) proper temperature maintenance, (b) promotion of breastfeeding, and (c) maintenance of adequate asepsis and infection control measures.
- *Timely referral* to higher center.

In National Heath Mission (India Newborn action plan), each birthing facility must have as *Newborn care corner (NBCC)* for level I care, to identify and refer at risk or sick babies to higher centers.

Level II care is required in 15–20% newborns with: (a) birth weight 1500–2000 gm, (b) gestation 32–36 weeks, (c) referrals from level I care, and (d) neonatal problems, e.g. mild/moderate birth asphyxia, Rh incompatibility, common malformations, respiratory distress and maternal diabetes.

It requires pediatrician's supervision and continuous nursing care but not the extensive investigations and intensive care. It should be available at all district hospitals, major and teaching hospitals and nursing homes, dealing with more than 1000–1500 deliveries annually. Important components of level II care include:

- Delivery attended by a trained pediatrician, with adequate resuscitation facility,
- Neonatal care by trained nursing staff, under a pediatrician's supervision
- Facility to provide warmer care, phototherapy, IV infusions/drugs, etc.

In National Heath Mission (India Newborn action plan), each first referral units, e.g. community health centers, must have *Newborn stabilization units (NBSU)* at block level and *Special newborn care unit (SNCU)* at district levels.

Level III care is needed in ~ 5% newborns, mainly with—(a) birth weight < 1500 gm, (b) gestation <32 weeks, (c) referrals from level II care, and (d) serious neonatal complications, e.g. severe birth asphyxia, major congenital malformations, severe respiratory distress, etc. NICUs should be available at select regional centers or in hospitals with >3000 deliveries per year, with following facilities:

- Round the clock availability of pediatrician/neonatologist and trained nursing staff.
- Round the clock availability of allied facilities, e.g. pediatric surgeons, blood bank and pathological/radiological investigations.
- Advance diagnostic, monitoring and therapeutic facilities, e.g. blood gas monitoring, drug delivery systems (infusion pumps) and procedures, e.g. exchange transfusion, peritoneal dialysis and total parenteral nutrition.

In National Heath Mission (India Newborn action plan), each district hospital or major centers must have *Special Newborn Care units (SNCUs) or Neonatal intensive care units (NICUs),* in addition to NBCC and NBSU.

Humanized neonatal care: In the current neonatal intensive care environment, a preterm or sick baby is subjected to many non-intentional noxious stimuli, which are believed to have adverse effects on his/her physiological stability and maturity. Humanized intensive care is not an alternative to high-tech care but is complimentary, to provide holistic care with a human touch, in a baby-friendly womb-like ambience in NICU.

Important components of this concept include:

- Minimum noise levels in NICU (leads to startle, apnea, HR/BP fluctuations)
- Minimum light exposure without compromising visual monitoring (excessive light exposure alters circadian rhythm and REM sleep).
- Prone/side-nursing positioning
- Minimum handling
- Breast or expressed breastfeeding
- Allowing the mothers in nursery.
- Gentle tactile stimulation/cuddling (*touch therapy*)
- Stimulation of special senses, e.g. auditory (soft music), visual (bright colored objects or maternal faces), olfactory (placement of cotton swabs soaked with mother milk in incubators).

Mother-neonatal intensive care unit (M-NICU) is novel concept in humanized neonatal care, where mother is permitted to stay next to the baby in NICU and is encouraged to participate in his/her care after some training, including Kangaroo mother care.

12.9 TRANSPORT OF A SICK NEWBORN

Transport of a sick newborn may be necessary for transfer to higher center (inter-facility transfer) or within the same center for investigation purposes (intra-facility transfer). Intra-facility transfer must be avoided, as far as possible. During the transfer, baby has to cope not only with primary illness but also with adverse environmental factors, e.g. cold, jerks, noise, etc., which can further compromise the survival.

It is always preferable to anticipate complications and transfer the high-risk baby *in utero*, though it is not

always possible due to logistic or medical reasons. In such cases, following principles should be observed to ensure safety of the baby.

- **Pre-transport preparations:**
  - Evaluate the genuineness of indication.
  - Communicate with parents about the reason for transport and get their consent.
  - Ensure availability of the vacancy at referral center and willingness to accept the transfer.
  - Arrange a well-equipped mode of transport, e.g. ambulance, well in advance.
  - Arrange a trained health-care provider to accompany the baby, who is well-versed with resuscitation procedures. Mother may also be encouraged to travel with baby.
  - Provide a detailed referral note, stating the reason for referral, pre-transport condition and treatment given along with necessary investigation reports.
  - Ensure availability and working condition of resuscitation equipments, including oxygen cylinder, etc. during trasnport
- **Stabilization of the baby:**
  - Resuscitate if required,
  - Ensure clear airway and breathing support during transport,
  - Correct hypothermia and ensure proper temperature support,
  - Secure good vascular access,
  - Give medications as required, till the baby reaches its destination.
- **During transport:**
  - Inform the referral center about expected time of arrival
  - Use the shortest and fastest route for transfer
  - Ensure proper ambient temperature in the vehicle
  - Do not open the windows or doors of the vehicle to avoid wind drafts
  - Continuously monitor the vital signs.
- **Hand-over the baby:**
  - Re-evaluate the baby before hand-over to referral team
  - Hand-over the baby, referral note and all left-over medicines, etc. to proper person
  - Inform them about any emergencies/changes during the travel time.
  - Counsel anxious parents and introduce them to the new team
  - Take the acknowledgement of transfer from new team including their assessment on arrival for records.

12.10 BIRTH INJURIES

Birth injuries are defined as *avoidable and unavoidable mechanical or hypoxic-ischemic injury, incurred by an infant during labor and delivery*. This definition excludes all injuries before the onset of labor during procedures, e.g. amniocentesis, *or* after delivery, i.e. during resuscitation.

TABLE 12.15: Risk factors for birth asphyxia/injuries

- **Maternal factors**
  - Cephalopelvic disproportion
  - Maternal sedation
- **Obstetric factors**
  - Prolonged or precipitate labor
  - Abnormal presentations
  - Uterine dystocia
  - Unattended/unskilled delivery
  - Meconium aspiration
- **Fetal factors**
  - Macrosomia
  - Prematurity/postmaturity
  - Congenital malformations

As the definition suggests, birth injuries may be classified into two categories—(a) birth asphyxia or hypoxic-ischemic injury, and (b) mechanical injuries.

Some important risk factors for hypoxic or mechanical birth injuries are given in **Table 12.15**. Apart from immediate problems, birth injuries are one of the most important causes of physical/mental handicap in later life.

12.10.1 BIRTH ASPHYXIA

Birth asphyxia (perinatal asphyxia) denotes *clinicopathological consequences of perinatal hypoxic-ischemic injury, due to late fetal, obstetrical or immediate postnatal causes*.

Diagnostic criteria for birth asphyxia depend on the purpose of diagnosis. While simplistic definition by National neonatology forum (NNF), i.e. *gasping, inadequate or no breathing at 1 minute* is appropriate to assess the immediate needs of resuscitation, many of these newborns recover completely after adequate resuscitation, without residual neurological deficits.

For the purpose of long-term outcome, American Academy of Pediatrics suggests following essential diagnostic criteria for perinatal asphyxia:

- Persistence of Apgar score 3 at 5 minutes,
- Fetal acidosis, i.e. cord blood pH <7.0,
- Signs of hypoxic-ischemic encephalopathy, e.g. seizures, coma, hypotonia, etc.
- Signs of multi-organ dysfunction.

Pathophysiology of birth asphyxia is multifactorial and complex—the common denominator *being lack of oxygen supply to various fetal tissues* during intrauterine, peripartum or immediate postnatal period. Intrauterine hypoxia is perhaps more important than the intrapartum asphyxia in causation of hypoxic-ischemic injury.

Immediate response to hypoxia in fetus or newborns is similar to that seen in older children, i.e. bradycardia and hypertension (*diving-seal reflex*), followed by a series of compensatory or protective events *as follows*:

a. *Re-distribution of blood flow* from less vital to vital organs, e.g. brain, heart and adrenals. Intra-cerebrally

TABLE 12.16: Multi-organ dysfunction in birth asphyxia

• CNS	HIE, IVH/PVH, cerebral edema
• CVS	Myocardial ischemia, hypotension
• Lungs	Pulmonary hypertension, hemorrhage, RDS
• Renal	Acute tubular/cortical necrosis
• GIT	Hemorrhage, stress ulcerations
• Blood	Disseminated intravascular coagulation (DIC)
• Metabolic	SIADH, hypoglycemia, hypocalcaemia
• Others	Adrenal hemorrhage

HIE: Hypoxic-ischemic encephalopathy, **IVH/PVH:** Intra/peri ventricular hemorrhage, **SIADH:** Syndrome of inappropriate ADH secretion, **RDS:** Respiratory distress syndrome

too, blood flow is re-distributed towards brainstem from cerebral cortex.

b. *Compensatory autonomic response* which is primarily sympathetic in term babies (↑HR, BP) and parasympathetic (↓ HR, BP) in preterms.

c. *Compensatory metabolic responses*, i.e. switch-over from aerobic to anaerobic metabolism.

However, prolonged hypoxia and consequent acidosis leads to many adverse pathophysiological changes, responsible for multi-organ dysfunction **(Table 12.16)**.

Diagnosis of birth asphyxia may be evident even before the delivery with signs of fetal hypoxia, e.g. bradycardia, altered fetal movements, meconium stained liquor, etc.

Postnatally, these cases are either apneic or have inadequate spontaneous breathing with persistently low Apgar score (3), cyanosis or pallor (*Asphyxia livida or Asphyxia pallida*), bradycardia and poor peripheral perfusion or hypotension.

Neurological damage in asphyxiated newborns varies according to the gestation age, generally presenting as *Hypoxic-ischemic encephalopathy (HIE)* in term neonates, and *Intraventricular-periventricular hemorrhage (IVH/PVH)* in preterms, as follows:

Hypoxic-ischemic encephalopathy (HIE): The term HIE refers to various "neuro-pathological changes and their clinical consequences in asphyxiated newborns, especially in *term or near-term babies".*

Pathogenesis of HIE is complex but main contributory factors include:

- *Increased neuronal cell permeability* due to hypoxia and acidosis.
- *Immature autoregulation of cerebral blood flow*, i.e. parallel changes with systemic blood pressure, leading to cortical hemorrhage in hypertensive states or ischemia/infarcts in hypotensive states.
- *Secondary necrosis* in hemorrhagic/ischemic areas, leading to neuronal loss and gliosis.
- Late development of focal/multicystic leukomalacia, porenchephalic cysts, cortical atrophy and *status marmoratus* (gliosis with hypermyelination) amongst survivors, with long-term sequelae.

TABLE 12.17: Severity grading for HIE

	Stage		
	I	***II***	***III***
Sensorium	Alert	Lethargic	Stupor/coma
Tone	N/↑	Hypotonia	Flaccid
Reflexes	↑	↑	Absent
Seizures	Absent	++	Decerebration
Moro's reflex	Strong	Weak	Absent
Pupils	Dilated	Constricted	Non-reacting
EEG	Normal	Abnormal	Burst suppression
Duration	<24 hours	2–14 days	>14 days
Outcome	Good	Variable	Death/sequelae

*or Isoelectric

Neuropathological changes in HIE also vary with gestational age, usually limited to watershed area (border-zones between areas supplied by different cerebral vessels) in fullterms, e.g. deeper cortical tissues in parasagittal region. Preterms have more diffuse pathology, also involving sub-cortical region specially in periventricular area and often associated with IVH.

Clinical manifestations of HIE may be apparent at birth or develop gradually, depending on the timing and severity of hypoxic insult. Common indicators of HIE include:

- Unresponsiveness to stimulation with sluggish reflexes,
- Hypotonia that may persist or change to hypertonia in a few hours, and
- Seizures, which may be multifocal, recurrent and/or refractory.

Severity of HIE may be graded according to *Sarnat and Sarnat classification* **(Table 12.17)** for prediction of outcome.

Diagnosis of HIE is mainly clinical in a full-term newborn with history of birth asphyxia, supported by:

- *Neuroimaging studies*, e.g. USG, CT/MRI. MRI is the preferred investigation and early neuroimaging findings include—(a) cortical infarcts, (b) cerebral edema, (c) intraventricular hemorrhage; while later studies may reveal, and (d) cortical atrophy and (e) focal/multicystic leukomalacia and/or porencephalic cysts.
- *EEG* has a prognostic significance with presence of isoelectric or burst-suppression patterns suggestive of moderate to severe HIE.
- *Lumbar puncture* is used to exclude meningitis and subarachnoid/intraventricular hemorrhage. Brain-specific creatinine kinase level (CK-BB) in CSF is a useful indicator of the severity of neuronal injury.

Management of HIE is supportive and involves:

- *Cardiopulmonary support* to ensure adequate ventilation (O_2, assisted ventilation) and perfusion (vasopressors,

volume expanders). A systemic mean arterial blood pressure of 45–50 mm Hg in term babies (35–40 mm in babies weighing 1–2 kg and 30–35 mm in those < 1 kg) is advisable.

- *Fluid restriction* to reduce cerebral edema and manage SIADH, preferably with 60 ml/kg/day of DW 10%.
- *Anticonvulsants* to prevent seizures and further neurological damage. Phenobarbitone is the preferred anticonvulsant in HIE and high-dose prophylactic phenobarbital may decrease neurodevelopmental impairment in these cases. Second-line anticonvulsants, e.g. Phenytoin or Levetiracetam should be added in refractory cases and stopped once the baby is seizure-free for > 72 hours. Phenobarbitone must be continued till discharge or even later, till the baby is neurologically normal. EEG may be used to decide the need to continue Phenobarbitone is doubtful cases.
- *Monitoring and control of other complications*, e.g. hypothermia, hypoglycemia, hypocalcemia, dyselectrolytemia and coagulation abnormalities.
- *Therapeutic hypothermia* to maintain the core temperature at 33.5°C during first 48–72 hours of birth, has been reported to reduce the mortality or neurodevelopmental morbidity in HIE, due to decrease in release of neurotoxic mediators, e.g. glutamate, free radicals, nitric oxide, lactate, etc. Complications include thrombocytopenia, bradycardia, subcutaneous fat necrosis and overcooling with cold-injury syndrome.

While emerging as a preferred intervention for HIE in developed countries, efficacy and safety of induced hypothermia has not been established in Indian settings and NNF recommends that it should be used only in a tertiary care setting under supervision by a trained team and only in selected group of newborns.

Efficacy of newer therapeutic modalities, e.g. free radical scavengers/removers, e.g. allopurinol or vitamin E; cerebral flow stabilizing agents, e.g. phenobarbital or calcium channel blockers, etc. is still in experimental stage.

Outcome depends on the severity of HIE, gestational age and co-existing complications. While most cases with Grade I HIE recover fully, grade II and III disease has progressively higher mortality (~ 5% and ~75%) and late neurological sequelae (~20% and ~100%).

Important neurological *sequelae* are—(a) cognitive deficits or mental retardation, (b) motor deficits, e.g. *cerebral palsy*, (c) epilepsy, (d) visual or hearing loss, and (e) hydrocephalus.

Apart from clinical staging, other *poor prognostic indicators* include—(a) HIE in a preterm baby, (b) low Apgar score or absence of spontaneous respiration at 20 minutes, (c) persistence of abnormal neurological signs at 2 weeks of age, and (d) abnormal EEG or CT scan.

12

Intra/periventricular hemorrhage (IVH/PVH) is primarily a neurological complication of birth asphyxia in *preterms*, with incidence being inversely related to gestational age and birth weight, i.e. 60–70% in babies <1000 gm, 10–20% between 1000–1500 gm and rare in newborns >1500 gm or 34 weeks.

Pathogenesis: IVH is rarely present at birth and usually develops during first 3 days of life. Subependymal germinal matrix, i.e. lining of the ventricular walls, is susceptible for rupture and bleeding *in preterms* due to—(a) higher vascularity, (b) poor tissue support to vasculature, and (c) immature autoregulation of cerebral blood flow—a protective mechanism that prevents sudden changes in cerebral perfusion pressure on systemic pressure changes in sick babies. Bleeding in germinal matrix may extend into ventricles (IVH) to cause obstructive hydrocephalus, and/or outwards into cerebral parenchyma (PVH). PVH or periventricular infarcts due to ischemic/reperfusion injury may later progress to develop as *periventricular leukomalacia* (PVL).

Clinical manifestations depend on the severity of IVH/PVH and ~25% cases are asymptomatic. Others may present on 2–3rd day, with:

- Early signs, e.g. sluggish/absent Moro reflex, sluggish activity and hypotonia. Progressive pallor or sudden drop in hematocrit is an early indicator of IVH/PVH.
- Recurrent apneic spells, acidosis and shock.
- Feeble or high-pitched shrill cry, seizures, bulging anterior fontanel and progressive coma in severe cases. While mild cases recover in a few days, others may progressively deteriorate or have a waxing and waning course, due to re-bleeds.

Diagnosis may be confirmed and classified **(Table 12.18)** on USG, which is routinely indicated in all high-risk preterms <1500 gm on 3rd day and 2nd week of life. USG also helps to assess the course of disease, i.e. progression, arrest or regression of hydrocephalus and development of PVL or porencephalic cysts.

CT/MRI is indicated only in—(a) suspected cases with intra-parenchymal bleed/infarcts, and (b) term infants with more chances of subdural/subarachnoid hemorrhage.

Management includes: (a) supportive measures, e.g. control of seizures, shock and anemia, (b) reduction of intraventricular pressure by repeated lumbar punctures or ventriculostomy, and (c) evacuation of subdural hematoma, if present.

TABLE 12.18: USG criteria for severity of IVH (Volpe's Classification)

Grade	*USG finding*
I	Bleeding limited to periventricular area (germinal matrix)
II	IVH filling 10–50% of ventricle
III	IVH filling >50% of ventricle or ventricular dilatation
IV*	IVH with periventricular hemorrhagic infarct

*not a part of Volpe classification

Prognosis depends on the severity and location of bleed. Apart from early death, *complications* include-(a) post-hemorrhagic hydrocephalus, and (b) residual sequelae due to PVL/porencephalic cysts, e.g. motor deficit, e.g. *cerebral palsy*, mental retardation, seizures, etc. Posthemorrhagic hydrocephalus, though develops in 10–15% babies with IVH, often gets arrested after a few days/weeks and most cases do not require shunting.

12.10.2 MECHANICAL BIRTH INJURIES

Incidence of mechanical birth injuries in India is estimated to be ~ 2–7/1000 live births, accounting for ~ 2–3% of neonatal deaths **(Table 12.19)**. Some important mechanical birth injuries are as follows:

Caput succedaneum is a diffuse, edematous and often ecchymotic *swelling of the soft tissue* covering the presenting part, e.g. scalp or face, which may extend across midline and sutures. It disappears spontaneously within a few days of life and no treatment is necessary.

Cephalohematoma is a *sub-periosteal hemorrhage*, essentially limited by sutural lines and presenting as unilateral (or rarely bilateral) soft and fluctuant scalp swelling. Swelling usually appears after a few hours of birth due to slower bleed in confined space, enlarges for few days and reabsorbs spontaneously in 3–6 weeks.

Incidence: It is seen in 1–2% of deliveries, more common in obstructed labor, forcep deliveries or vacuum extractions.

TABLE 12.19: Common mechanical birth injuries

- **Cranial injuries**
  Caput succedaneum
  Cephalohematoma
  Skull fractures (linear/depressed)
  Intracranial hemorrhage
- **Cervical injuries**
  Cervical spinal injuries
  Sternocleidomastoid tumor
- **Peripheral nerve injuries**
  Brachial plexus injury
  Erb-Duchenne paralysis
  Klumpke's paralysis
  Phrenic nerve injury
  Facial palsy
- **Limb injuries**
  Fractures (clavicle, humerus, femur)
  Dislocation of upper femoral epiphysis
- **Visceral injuries**
  Liver (subcapsular hematoma)
  Splenic rupture/hematoma
  Adrenal hemorrhage
- **Superficial Soft-tissue injuries**
  Skin abrasions, laceration, ecchymosis
  Genitals: Scrotal hematoma, hematocele
  Eye: Subconjunctival hemorrhage
  Retinal/vitreous hemorrhage

Diagnosis is obvious clinically, but may be confirmed on X-ray skull that reveals subperiosteal bleed and rarely, an underlying linear skull fracture **(Fig. 12.7)**.

D/D includes *caput succedaneum* **(Table 12.20)** and *cranial meningocele* (pulsatile, increases on crying, underlying bony defect on X-ray).

Complications are uncommon but include—(a) anemia, (b) hyperbilirubinemia, (c) infection, if erroneously aspirated.

Management: *Aspiration or surgical drainage is contraindicated*, to avoid the risk of infection. No intervention is needed in small hematomas, though babies with large swellings should be observed and treated for complications, e.g. severe anemia or hyperbilirubinemia.

Brachial plexus injuries are common in large babies, specially when excessive lateral traction is applied to deliver shoulder in vertex deliveries or extended arm in breech deliveries.

Clinically, these injuries may present as upper-plexus (*Erb-Duchenne paralysis*) or lower-plexus (*Klumpke's paralysis*) injury or both.

- **Erb-Duchenne paralysis,** i.e. injury to upper roots of brachial plexus (C_{5-6}) is characterized by:
  - *Abnormal limb position with* adducted and internally rotated arm with pronated forearm (*Policeman stick appearance)*, due to weakness of abductors, external rotators and supinators **(Fig. 12.8A)**.
  - *Asymmetrical Moro's reflex* (d/d fracture, osteomyelitis/ arthritis, dislocation)

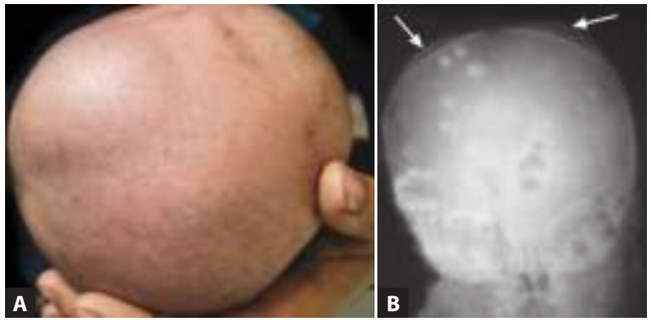


Fig. 12.7: Cephalhematoma: (A) Clinical appearance; (B) X-ray skull.

TABLE 12.20: Caput succedaneum *vs* cephalohematoma

	Caput succedaneum	*Cephalohematoma*
Location	Soft tissue	Sub-periosteal
Extent	Diffuse	Limited by sutures*
Onset	At birth	Few hours after birth
Color	Ecchymotic	Skin colored
Disappears	< 7 days	> 3–6 weeks
X-ray skull	Normal	± Linear fractures
Complications	Very rare	Anemia, jaundice

*unless underlying fracture is present

Figs. 12.8A and B: **Brachial plexus injury: (A) Erb's palsy; (B) Klumpke's palsy.**

  - Normal power in forearm (except pronation) and hands with *preserved grasp reflex*
  - Associated ipsilateral diaphragmatic paralysis due to phrenic nerve palsy ($C_{3–5}$) in some cases.
- **Klumpke's paralysis,** due to lower-plexus injury ($C_{7–8}$ T_1) is relatively rare, presenting with:
  - Weakness of wrist and hand movements with abnormal position (*Accoucher's grip*) **(Fig. 12.8B)**
  - *Absent grasp reflex*.
  - Associated *Horner syndrome* (ptosis and miosis on affected side) due to injured T_1 sympathetic fibres.

Management of brachial plexus injuries involves-(a) intermittent immobilization with splints in neutral position to prevent contractures during first 1–2 weeks, and (b) gentle massage with increasing range of motion exercises after 7–10 days. Recovery is unlikely beyond 6 months, when neuroplasty or nerve grafting must be considered.

Prognosis depends on whether the nerve fibers are merely injured (recovery in 2–3 months) or truly lacerated (permanent functional loss). Upper plexus injury has better prognosis than lower plexus injury. A intact gasp reflex suggests > 80% chances of recovery.

Skull fractures are common during breech or instrumental deliveries and may be linear or depressed. Some fractures may be associated with intracranial bleeding. No treatment is necessary for linear fractures without intracranial hemorrhage, while depressed fractures need neurosurgical assessment.

Clavicular fractures are most common bony injuries in macrosomic babies, delivered with shoulder or breech presentation. These babies present with restricted movement of affected arm (pseudoparalysis) with asymmetric Moro's reflex. No intervention is required except splinting and healing usually occurs in 2–4 weeks.

Intracranial hemorrhage in newborns may be broadly divided into 2 types:

a. **Subdural, epidural or subarachnoid hemorrhage**, are more common in term newborns, usually caused by (a) mechanical head injury in obstructed labor, precipitate deliveries or forceps application, (b) bleeding disorders, e.g. DIC, immune thrombocytopenia, etc. and (c) intracranial vascular malformations.

   These cases usually present with recurrent seizures, progressive head enlargement with bulging fontanels and anemia in late neonatal period. Diagnosis may be confirmed on USG or CT scan. Surgical evacuation of hematoma is indicated only in symptomatic cases.

b. **Intraventricular/periventricular hemorrhage**, is mostly seen in *preterms with birth asphyxia*, discussed earlier in Ch 12.10.1.

Sternocleidomastoid tumor (Torticollis) is actually a *sub-facial or intramuscular hematoma in sternocleidomastoid muscle* due to over-stretching and laceration of muscle fibers during delivery of impacted head in breech/shoulder deliveries. Some cases are also thought to be hereditary or *in utero* muscle infection.

Clinically, these cases present on 10^{th}–14^{th} day with:

- A *well-circumscribed, non-tender small mass* (1–2 cm) over mid-sternocleidomastoid muscle, which gradually enlarges for 2–4 weeks, before regressing completely by 6–8 months **(Fig. 12.9)**.
- *Torticollis* with head tilted on same side and chin elevated and rotated on opposite side. Torticollis usually disappears with mass, but may persist for many years due to residual scarring and leads to secondary deformities, e.g. craniofacial asymmetry, scoliosis and gaze abnormalities.

Fig. 12.9: **Sternocleidomastoid tumor.**

Treatment includes frequent gentle over-stretching of the neck on opposite side (taught to mother) in early months and bed-time splinting in corrected position. Surgical lengthening by division of sternal portion of muscle is indicated only in persistent torticollis beyond 6–8 months.

12.11 GESTATION AND BIRTH WEIGHT DISORDERS

Low birth weight (LBW) refers to the babies weighing with < 2500 gm at birth, while those <1500 gm and <1000 gm at birth are termed very low birth weight (VLBW) and extremely low birth weight (ELBW).

Based on the intrauterine growth and position on the intrauterine growth charts **(Fig. 12.10)**, all babies at birth may be classified, irrespective of the gestation, as:

- *Appropriate for date (AFD)*, i.e. birth weight within the normal limits (10^{th}-90^{th} percentile) for gestation
- *Small for dates (SFD)*, i.e. birth weight less than normal (<10^{th} percentile) for gestation
- *Large for date (LFD)*, i.e. birth weight more than normal (>90^{th} percentile) for the gestation.

However in practice, LBW, irrespective of the gestation, has been identified as the most important markers of adverse perinatal and neonatal outcome in India, with reported rate of ~18% as per recent NFHS-5,2021. Since gestational age is main determinant of birth weight, the term LBW encompass both – preterm LBW and term LBW, discussed in following sections.

12.11.1 PREMATURITY (PRETERM-LBW)

Prematurity is defined as a *live birth before the completion of 37th week of gestation* (up to 36 weeks and 6 days). Live births before 28th week are generally referred as *extreme prematurity*.

Causes: Preterm labor may be *spontaneous* due to various maternal and fetal factors or *induced* on medical grounds **(Table 12.21)**. Many spontaneous preterm labors are preventable by timely medical care.

TABLE 12.21: Causes of prematurity

- **Maternal ill health**
  - Chronic systemic diseases
  - Severe anemia
  - Infections of genitourinary tract
- **Uterine abnormality**
  - Incompetent cervix
  - Bi-cornuate uterus
- **Obstetric complications**
  - Twin pregnancy
  - Antepartum hemorrhage, placenta previa
  - Poly-/oligohydramnios
  - Premature rupture of membranes
- **Fetal factors**
  - Fetal hypoxia and distress
  - Hydrops fetalis
  - Serious congenital malformations
- **Idiopathic**

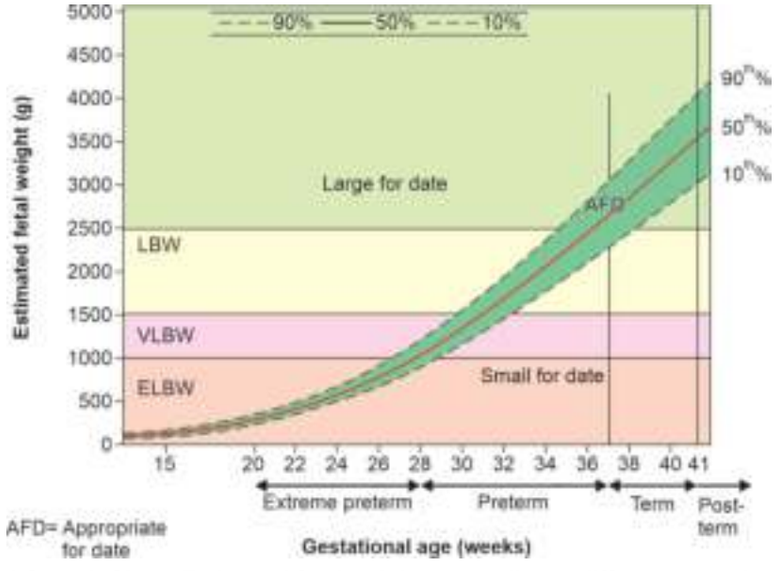


Fig. 12.10: **Fetal Growth Chart: Estimated fetal weight percentiles at different gestational ages (WHO).**

TABLE 12.22: Common clinical and neurological features at different gestational ages

Clinical features	*<28 weeks*	*28–32 weeks*	*32–36 weeks*	*Full-terms*
Physical				
a. Breast nodule	Nil	<5 mm	5–10 mm	>10 mm
b. Ear cartilage	Crumpled/no recoil	Soft/some recoil	Firm/good recoil	Firm/instant recoil
c. Plantar creases	Nil	Faint, anterior sole	Deep, transverse only	criss-cross, all sole
d. Skin				
– Appearance	Thin, gelatinous	Hyperemic	Thick, dry	Thick, peeling ±
– Vernix	All over	All over	Reduced	Flexural only
– Lanugo	None	+++	++	Scanty
e. Male genitals				
– Scrotum	Shiny, red	Rugosities +	Darker, rugosities ++	Dark, rugosities +++
– Testis	B/L undescended	At least 1 in Ing. canal	At least 1 in scrotum	B/L descended*
f. Female genitals				
– Labia majora	Covers <1/3rd minora	Covers >1/3rd minora	Covers >2/3rd minora	Covers whole minora
Neurological				
a. Posture	Frog-like	Only arms flexed	Legs partly flexed	Well flexed
b. Arm recoil	Nil	Incomplete	Complete	Complete and brisk
c. Popliteal angle	180°	180–150°	150–120°	<120°
d. Scarf sign	Complete	Beyond midline	Only till midline	not reaching midline
e. Heel to ear	Reaches up to ear	Reaches up to neck	Reaches up to waist	Doesn't touch waist
f. Square window	90°	60°	30°–45°	None

Clinical attributes of prematurity vary with gestational age **(Table 12.22)**, though some important indicators are as follows:

- **Physical features** in preterms include:
  - ***Skin*** *is shiny, hyperemic,* covered with plenty of *vernix caseosa (a* whitish greasy substance to prevent hypothermia) and *Lanugo* (soft-fuzzy hair on back and limbs). *Pedal edema* is common in extreme preterms.
  - ***Sole creases*** are absent or poorly developed, seen in only some parts of soles.
  - ***Ear cartilage*** is poorly formed and shows slower recoil, when crumpled. Eyes are tightly closed in extreme preterms.
  - ***Breast nodule****,* felt as an induration by rolling-over between fingers, is poorly developed.
  - ***Genitals:*** In *male preterms,* scrotum is shiny and less pigmented with poorly developed scrotal rugosities and undescended or partially descended testis. *In female preterms*, labia majora is widely separated to covers only a part of labia minora. In fullterms, labia minora is almost invisible.
- **Neurological features** in preterms include:
  - ***Posture:*** Preterms have a prominent head lag and stay in a *pithed-frog posture* with extended limbs due to marked hypotonia, as against the fully-flexed fetal posture in fullterm.
  - ***Hypotonia*** is a prominent feature in preterms, as evident by their posture as well as when tested for active tone (poor arm recoil) and passive tone (popliteal angle, Scarf sign or heel to ear maneuver).
    - *Popliteal angle* is measured behind the knee on complete flexion at hip and maximum extension at knee.
    - *Scarf sign* is tested by adducting one upper arm towards opposite shoulder and checking the position of elbow on full adduction.
    - *Heel to ear* maneuver involves an attempt to touch the ear with baby's heel and *see* its maximum possible reach.
  - *Immature joint mobility,* as indicated by *Square window sign*. *Square window* is the angle formed at wrist after complete flexion to touch the forearm with fingers.
  - *Immature neonatal reflexes,* which appear gradually with advancing gestation **(Table 12.12)**.

Assessment of gestation age depends on—(a) date of last menstrual period, (b) antenatal records, e.g. fundal height and USG, and (c) physical and neurological features of newborn. Birth weight is not a reliable criteria for diagnosis of prematurity, as it does not exclude SFD/IUGR babies.

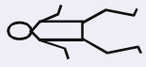
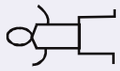
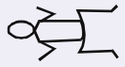
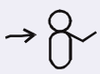
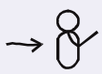
Various scoring systems, based on physical and neurological features, e.g. *Dubowitz criteria* or *Ballard scoring* **(Table 12.23)** are available for precise postnatal assessment of gestation age.

TABLE 12.23A: Modified Ballard scoring system for assessment of gestational age

A. PHYSICAL CRITERIA

Score →	–1	0	1	2	3	4	5
Skin	Sticky, friable transparent	Gelatinous, red, translucent	Smooth, pink, visible veins	Peeling, rash, few veins	Cracking, pale, rare veins	Parchment deep cracks, no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	—
Plantar surface	HTL <50 mm (<40 mm; –2)	HTL >50 mm No creases	Faint red marks	Ant. transverse crease	Creases in ant 1/3rd	Creases on entire sole	—
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stripped areola, 1–2 mm bud	Raised areola, 3–4 mm bud	Full areola 5–10 mm bud	—
Eye/ear	Eye lids fused Loosely: –1 Tightly: –2	Eye lids open, pinna flat, stays folded	Slight curved pinna, soft, slow recoil	Well-curved pinna, soft but ready coil	Firm pinna instant recoil	Thick cartilage, stiff ear	—
Genitals *(male)*	Scrotum flat and smooth	Scrotum empty, faint rugae	Testes in upper canal rare rugae	Testes descending, few rugae	Testes down, Good rugae	Testes pendulous, deep rugae	—
Genitals *(female)*	Clitoris prominent, labia flat	Prominent clitoris, small L. minora	Prominent clitoris, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Major covers clitoris and minora	—

B. NEUROLOGICAL CRITERIA

Posture	—						—
Square window (wrist)	90°	90°	60°	45°	30°	0°	—
Arm recoil	—	180°	140–180°	110–140°	90–110°	<90°	—
Popliteal angle	180°	160°	140°	120°	100°	90°	<90°
Scart sign							—
Heal to ear							—

HTL: Heel-Toe length
Methodology: Calculate the total score by adding individual scores on each physical (A) and neurological (B) parameters as per **Table 12.26 A** and then assess gestational age (in weeks) by using following **Table 12.23**.

TABLE 12.23B: Gestational maturity as per new Ballard score

Score	–10	–5	0	5	10	15	20	25	30	35	40	45	50
G. Age	20	22	24	26	28	30	32	34	36	38	40	42	44

Physiological handicaps and complications: A premature child has many physiological immaturities or handicaps, rendering him susceptible for many complications in immediate postnatal or later life **(Table 12.24)**. Important handicaps include:

- ***Thermoregulation immaturity*** *(hypothermia)* due to-(a) excessive heat loss via larger surface area and thin skin, and (b) poor heat production due to less brown fat.
- ***Respiratory immaturity*** with *poor*-(a) central control (*apneic spells*), (b) cough-reflex *(aspiration pneumonia)*,

TABLE 12.24: Complications of prematurity and LBW

		Preterms	*FT/SFD*
a.	***Asphyxia (perinatal)***		
	HIE	+	++
	IVH/PVH	+++	+
b.	***Breathing (respiratory)***		
	Hyaline memb. disease	+++	–
	Apneic spells	+++	–
	Meconium aspiration	+	++
	Postnatal aspiration	+++	+/–
	Pulmonary hemorrhage	+	+++
c.	***Cong, malformations***	+	+++
	PDA	+++	–
d.	***Hypothermia***	+++	+
e.	***Metabolic***		
	Hypoglycemia	+	+++
	Hypocalcemia	+++	+
	Kernicterus	+++	+
	Drug toxicities	+++	+
	Late metabolic acidosis	+++	+
f.	***Gastrointestinal***		
	Feeding difficulties	+++	+/–
	Necrotizing enterocolitis	+++	+/–
g.	***Hematological***		
	Anemia	+	++
	Polycythemia	+	++
	Hematologic disease of newborn	+	++
h.	***Infections***		
	Postnatal infections	+++	+
	Intrauterine infections	+	+++
i.	***Outcome***		
	Immediate	Poor	Good
	Long-term growth	Good	Poor
	Other late complications*	++	+

*e.g. Cerebial palsy, mental retardation, retinopathy of prematurity, broncho-pulmonary dysplasia
IVH/PVH: Intraventricular/periventricular hemorrhage,
HIE: Hypoxic-ischemic encephalopathy

(c) ventilatory efforts due to highly compliant chest wall, (d) alveolar expansion due to surfactant deficiency *(hyaline membrane disease)*, (e) alveolar diffusion due to cuboidal epithelium, and (f) perfusion due to trans-PDA shunting.

- ***Circulatory immaturity*** with—(a) delayed closure of ductus arteriosus *(PDA)*, (b) increased vascular permeability, and (c) immature autoregulation of cerebral blood flow *(IVH/PVH)*.
- ***Neurological immaturity*** with—(a) generalized hypotonia/hyporeflexia, (b) immature germinal matrix *(IVH/PVH)*, and (c) impaired blood–brain barrier (*Kernicterus*). However, hypoxia is better tolerated by preterms than term babies.
- ***GIT immaturity*** with *poor*—(a) sucking/swallowing reflexes *(feeding difficulties)*, (b) palato-pharyngeal competence *(recurrent aspiration)*, (c) esophageal sphincter competence *(gastroesophageal reflux)*, (d) gastric volume *(inability to tolerate large feeds)*, (e) digestive enzymes, e.g. lipase, trypsin and lactase, activity *(digestive/absorptive problems)*, and (f) intestinal motility and stasis *(gut infections)*.
- ***Hepatic immaturity*** with *poor*—(a) glucuronyl transferase activity *(hyperbilirubinemia)*, (b) nutrient metabolic activity *(hypoglycemia, hypoproteinemia)*, and (c) drug metabolism *(increased risk of toxicity)*.
- ***Renal immaturity*** with *poor*—(a) glomerular filtration rate *(solute overload, drug toxicity)*, (b) urinary concentration *(dehydration)*, (c) sodium conservation *(hyponatremia)*, and (d) acidification capacity *(late metabolic acidosis)*.
- ***Immunological incompetence*** *(infections)* due to—(a) low IgG levels via maternal transfer, (b) low secretary IGA, phagocytic, complement activity, and (c) impaired cell-mediated immunity.
- ***Hematological immaturities*** with—(a) poor iron stores *(apnea of prematurity)*, (b) deficiency of clotting factors (*bleeding tendencies*).
- ***Nutritional problems*** due to—(a) poor stores *(hypoglycemia, hypocalcemia)*, (b) higher requirements due to higher surface area, tissue turnover, catch-up growth, etc. and (c) poor intake.
- ***Endocrinal immaturity***, e.g. transient hypoparathyroidism *(osteopenia of prematurity)*.

Management of a preterm child begins before birth, including—(a) delaying elective preterm deliveries as long as possible, and (b) referral to well-equipped centers, (c) antenatal steroids, to enhance lung maturity. All preterm deliveries should be attended by trained neonatologist and delayed clamping of cord helps not only to improve iron stores but also to reduce the risk of intraventricular hemorrhage and other morbidities.

While Borderline preterms may be managed as term babies, postnatal management of a preterm baby depends on the gestational age, birth weight and presence of complications. While borderline preterms can be managed as term babies only, most babies weighing < 2000 gm or 34 weeks of gestation need careful consideration for physiological handicaps and potential complications. Important steps include:

a. **Intensive care:** All preterms <1500 gm, <32 weeks or with complications, e.g. infections or congenital malformations, need to be hospitalized in level-III NICU. More mature babies without major problems may be managed in level-II nursery, provided constant monitoring is possible.
b. **Thermoregulation** is the most important determinant for survival during first 24 hours. All preterm babies should be prevented from hypothermia by appropriate

measures, depending on their clinical gestation and clinical status, as follows:

- ***Kangaroo mother care (KMC)*** be initiated immediately after birth in babies in all borderline preterms/LBWs, weighing >1800 gm, provides they are otherwise stable and have no other complications. Proper 2–3 layer clothing including mittens and cap is required during intervening period.
- ***Warmer-care*** is usually required in babies < 1800 gm as well as all sick/unstable LBWs, providing a thermoneutral environment to minimize oxygen and metabolic requirements. Ideal thermoneutral environment varies with gestational age, though ~33–35°C is adequate for most preterms (Ch 12.12). However, most of them, specially those between 1200–1800 gm can also be shifted to KMC after few days of observation and stabilization.
- Temperature control is also necessary during transfer of these babies from delivery room to NICU as well as during investigations and blood sample collections.
- Body temperature must be monitored frequently in all preterms, using an axillary digital thermometer, at least 2–4 hourly on the first day of life.
- Relative humidity must be maintained at 40–60% to prevent drying of airways, thickening of secretions and insensible water loss from the lungs.

c. **Nursing position:** It is preferable to keep these babies in prone position (except immediately after feeding and when sick) to facilitate drainage of oropharyngeal secretions (prevents aspiration), passage of flatus (less abdominal distension) and lesser effort for ventilation. However, many workers advise supine position for ease of clinical supervision.

d. **Nutrition:** Quantity and mode of feeding is an important issue in preterm care due to—(a) higher nutritional requirements, and (b) physiological immaturity in sucking, swallowing, digestion and absorption of feeds.

Nutritional requirements of these babies vary with gestation, weight, nursing environment and associated complications, as follows:

- *Higher fluid requirements* **(Table 12.25)** due to high basal metabolic rate well as excessive losses via kidney (physiological diuresis), GIT (physiological diarrhea), lungs (physiological tachypnea) and skin (large surface area).
- *Higher energy requirements* coupled with inability to accept large volume feeds. Preterm feeds should provide ~130 cal/kg with higher caloric density of ~70 cal/100 ml.
- *Higher protein requirements* due to increased tissue synthesis and immature metabolism of essential amino acids. Consequently, preterm-feeds should provide ~ 2.5–3.0 gm/kg proteins, with whey:casein ratio of 60:40 (as in breast milk), and all essential amino acids in appropriate amounts.
- *Low lactose/starch digestibility*, due to physiological lactase/amylase deficiency. Carbohydrates should not exceed 40–50% of preterm feed, of which at least 50% should be as glucose polymers, e.g. maltodextrin, polycose.
- *Poor fat digestibility/absorption*, due to physiological deficiency of pancreatic lipase and bile salts. Medium chain triglycerides, e.g. coconut oil, which are directly absorbed in portal circulation without micelles formation, are better tolerated in preterms. As essential fatty acid deficiency is common in preterms, 1% of total energy should be provided by linoleic acid.
- *Higher sodium requirements* due to inadequate renal conservation capacity. A preterm feed should provide ~2.5–3.5 mEq/kg/d of sodium (4–8 mEq/kg in VLBWs).
- *Micronutrient supplementation* **(Table 12.26)** is necessary due to poor stores and higher requirements. However, iron supplements should be delayed till ~2–4 weeks, due to potential risk of hemolytic anemia (competitive vitamin E deficiency) and pathogenic diarrhea (iron binds lactoferrin-an inhibitor of *E. coli* growth).

While the precise mode of feeding depends on the acceptability by the baby, following general guidelines may be used for initial feeding decisions in different categories of preterms **(Table 12.27)**:

TABLE 12.25: Fluids requirement (ml/kg) in preterm/LBW

Day of life	*>1500*	*1000–1500*	*<1000*
1st	60	80	100
3rd	90	110	130
5th	120	140	160
7th	150	170	190

Simple thumb rules:
- Fluid needs in 3 weight categories differ by 20 ml.
- Daily requirements in each category increase by 15 ml/day

Add 20 and 40 ml/kg for babies under phototherapy and warmers respectively

TABLE 12.26: Essential nutrient supplements in preterms/LBW

Nutrient	*Daily dose (except vitamin K)*
Vitamin A	1000 IU
Vitamin D	400–800 IU
Vitamin K	0.5–1.0 mg **weekly**
Vitamin C	35 mg
Vitamin E**	5–25 IU
Folic acid	50 mg
Iron***	2–3 mg/kg
Calcium	220 mg
Phosphates	100 mg

*From 2 weeks onwards, except vitamin K (from birth)
**In VLBWs only, till 36 weeks maturity is reached
***After full enteral feeding established, not later than 8 weeks

TABLE 12.27: Modes of feeding in preterms/LBW

	Birth weight (gm)		
	<1200	***1200–1800***	***>1800***
Begin with	IV	Gavage	BF or K&S
Switch to (1–3 days)	Gavage	K&S	BF
Switch to (1–2 weeks)	K&S	BF	BF
At discharge	BF	BF	BF

K&S: Katori and spoon, **BF:** Breastfeeding

Uncomplicated preterms >1800 gm or >32 weeks usually accept breastfeeds and may be fed directly or via bondla/spoon by mothers.

Preterm milk is qualitatively different from term-milk on following counts-Low caloric density (51 vs. 67), high proteins (2.2 vs. 1.1 gm), low lactose (6.0 vs. 7.0 gm), low fat (1.6 vs. 3.5 gm), high sodium (2.6 vs. 0.7 gm) and high Ca/P ratio (20/10 vs. 34/15 mg). (All values/100 ml milk, composition changes with gestation)

Uncomplicated preterms 1200–1800 gm or 28–31 weeks usually require intragastric feeding of expressed breast milk (EBM) for first few days, followed by Bondla/spoon feeding or direct breastfeeds, as soon as acceptable.

It is advisable to begin with 60–80 ml/kg/d of EBM on first day (on lower side in better weight babies and increase by 15 ml/kg every day till ~150 ml/kg/d is reached. Volume of each feed may be calculated by dividing the total daily requirement with number of feeds.

Position of nasogastric tube should be checked before feeding, as also the amount of pre-feed aspirate, which should not exceed >1/3rd of previous feed. Increased pre-feed suggests poor gastric emptying—an early indicator of necrotising enterocolitis, intestinal obstruction or paralytic ileus.

Human milk fortifiers (HMF) are natural or commercial substances, used to improve energy content of EBM without significant volume load. These include *vegetable oils*, e.g. coconut oil or safflower oil (2–3 drops/20 ml feed) and *commercial preparations* (~ 2 cal/gm; 1 gm/10 ml feed). HMF may be used in uncomplicated infants < 1800 gm, after 1st week, to enhance caloric density of EBM.

Complicated or extreme preterms (<1200 gm or < 28 weeks) usually need parenteral nutrition for first 48–72 hours, provided as 60–80 ml/kg of 5% dextrose, higher side in lighter babies. Sodium and potassium must be added in IV fluid after 48 hours. Fluid requirements increase with increasing age as 10–15/ml/kg/day, to a maximum of 150 ml/kg/day after the first week.

While most preterms can be gradually switched on oral feeds, those who need parenteral nutrition for more than one week, must be considered for *total parenteral nutrition* (Ch 27.4.5).

Non-nutritive sucking or trial breastfeeding is advised to all babies on parenteral or nasogastric feeding, to promote lactation and emotional bonding. While the breast milk from own mother is best and gestation-specific for preterms, breast milk from milk-bank or other mothers may be used in cases with maternal death/serious illness. If it is inevitable to use top milk, only a preterm-specific formula milk must be used rather than term-milk formulas or animal-milk, to avoid solute overload and other complications.

e. **Monitoring:** All preterms should be constantly monitored for adequacy of feeding, weight gain and danger signals and IV sites. Non-invasive devices, e.g. apnea alarms and pulse oximeter are frequently used to monitor extreme/complicated preterms.

All babies in hospital must be weighed daily to assess adequacy of nutrition. Preterm babies loose ~15% of birth weight in first week (vs 10% loss in terms) and regain it by 10th-14th day (7–10 days in terms), followed by gaining ~15–20 gm/day, even 20–40 gm/day as they approach near term (catch-up growth). Fenton charts may be used to monitor infant's growth in preterms till they reach 50 weeks of gestational age.

f. **Prevention of nosocomial infections** requires: (a) restricted-entry in nursery, (b) minimal handling, (c) proper hand-washing, (d) ensuring asepsis during diagnostic/therapeutic interventions, and (e) early detection/treatment infections. Prophylactic antibiotics are not necessary in preterms, except those with other risk factors.

g. **Discharge criteria** for preterms include: (a) weight >1800 gm with steady gain, (b) absence of complications or need for parenteral medications, (c) adequate feeding with acceptance of direct breastfeeding or EBM with Bondla/spoon, (d) Complete age-appropriate immunization, (e) Adequate maternal counseling for general baby care, thermo-care, feeding and follow-up.

It is advisable to keep mother and baby in intermediate care or regular postnatal ward for a few days after discharge from NICU, to ensure baby's well-being.

Outcome of prematurity depends on its severity and presence of complications. With therapeutic advances, even babies as young as 22 weeks (>500 gm) are salvageable. However, survival of extreme preterms has also increased the risk of late sequelae in these babies and *Follow-up* of all preterms is necessary at periodic intervals till at least one year, to assess catch-up growth and identify late sequelae.

12.11.2 INTRAUTERINE GROWTH RETARDATION

The term intrauterine growth retardation (IUGR) or small for date (SFD) or Small for gestational age (SGA) is reserved for those LBW babies, who are born *fullterm*

TABLE 12.28: Causes of IUGR (small for date LBW)

- **Maternal factors** *(poor nutrition/chronic hypoxia)*
  - Age <20 or >35 years
  - *Parity:* Primipara or grand-multipara
  - Undernutrition or poor weight gain in pregnancy
  - Anemia
  - Chronic cardiac or pulmonary disease
  - *Abuse:* Drugs, alcohol, smoking
- **Placental factors** *(↓ uteroplacental blood flow)*
  - Structural abnormalities
  - Abruptio placentae
  - Vascular infarcts: Hypertension, pre-eclampsia
  - Multiple gestations (twin-twin transfusion)
- **Fetal factors** *(↓ growth potential)*
  - Chromosomal/genetic disorders, e.g. trisomies
  - Dysmorphic syndromes/congenital anomalies
  - Intrauterine infections
  - *Metabolic:* Insulin/insulin-like growth factor deficiency
- **Idiopathic**

or preterm, with birth weight 2 SD or 10th percentile for their gestation, thus excluding preterm-AGA.

Causes: Fetal growth depends on adequate transplacental supply of nutrients and oxygen from mother as well as on its inherent growth potential. Consequently, IUGR may be caused by:

- Maternal malnutrition or chronic hypoxic states, e.g. anemia, cardiopulmonary diseases, etc.
- Decreased placental blood flow due to placental abnormalities, or
- Decreased fetal growth potential, e.g. intrauterine infections or chromosomal disorders.

Maternal malnutrition, anemia and intrauterine infections are three leading causes of IUGR in India **(Table 12.28)**.

Clinical features: Clinical features of IUGR babies vary according to the timing of intrauterine insult and may be divided into 3 categories:

a. ***Symmetrical IUGR*** *(hypoplastic SFD),* due to fetal insult in first trimester, before organogenesis is complete. All growth parameters, e.g. weight, length and head circumference are proportionately affected in these babies, giving them a *tiny appearance* and *high ponderal index* >2. For ponderal index calculation, *see* footnote of **Table 12.33**.

b. ***Asymmetrical IUGR*** *(malnourished SFD),* due to fetal insult in late gestation. As fetal weight is disproportionately more affected than length or head circumference, these babies have a *marasmic* appearance with low ponderal index <2.

c. ***Mixed SFD,*** with adverse intrauterine factors operative throughout the gestation.

Diagnosis of IUGR may be suspected antenatally on the basis of: (a) discrepancy between gestational age by history and fundal height, and (b) USG findings, e.g. low BPD for gestation (<8.5 cm at 37 weeks), or fetal head-thorax or head-abdomen ratio. Important differences between asymmetric and symmetric IUGR are given in **Table 12.29**.

TABLE 12.29: D/D asymmetrical *vs* symmetrical IUGR

	Symmetrical	***Asymmetrical***
Timing of IU insult	Early	Late
Common cause	IU infections	Mat. malnutrition
Appearance	Tiny	Marasmic
Length and head circumference	Reduced	Near normal
*Ponderal index**	>2	<2
Malformations	Common	Uncommon
Cellular pathology	Hypoplasia	Hypotrophy
Growth potential	Poor	Preserved

***Ponderal Index:** Weight in gm/length in $cm^3 \times 100$

Complications: FT/SFD are physiologically as mature as normal term newborns and complications related to prematurity are uncommon despite low birth weight. However, these babies are more prone for (a) *perinatal asphyxia* due to placental dysfunction, (b) *hypoglycemia* due to poor stores, (c) *congenital malformations* due to intrauterine infections, (d) *hypothermia* due to scanty body fat, (e) *poor growth potential* in long-term.

PT-SFDs have additional risk of complications related to prematurity as enumerated in **Table 12.27**, which also summarizes important difference between complications in fullterm and preterm LBWs.

Management of IUGR is similar to that of preterms, as discussed in previous chapter, with following special considerations:

- *Delivery room care*—as IUGR babies are more prone for intrauterine asphyxia, regular fetal monitoring with emergency LSCS facility and neonatal resuscitation should be available.
- As these babies are prone for hypoglycemia, early breastfeeding should be ensured, with periodic glucose monitoring.
- Congenital malformations and stigmata of intrauterine infections should be carefully looked in FT-SFD cases.
- Polycythemia, if symptomatic, should be managed by partial exchange with plasma.

Outcome: Chances of immediate survival are better in FT-SFD babies than in preterms. However, growth potential is often reduced in them and unlike preterms, SFDs do not show catch-up growth, ultimately ending with short-stature.

12.11.3 LARGE FOR DATE BABIES

Babies, born with birth weight of >90th percentile or 2 SD for their gestation, are termed as *large for date* (LFDs) babies.

TABLE 12.30: Causes of *Large for Date Baby*

- Constitutional
- Maternal diabetes, ovarian tumors
- *Fetal:* Hypothyroidism, congenital adrenal hyperplasia
- *Chromosomal:* Wiedemann-Beckwith syndrome
- *Others:* Hydrops fetalis, cerebral gigantism

Causes: *Constitutional large size* and *infants of diabetes mother* (IDM) are most common causes of LFDs in India, apart from others **(Table 12.30)**. Some unique causes of LFD are as follows:

Wiedemann-Beckwith syndrome is probably a defect in chromosome 11, characterized by large body size (macrosomia), macroglossia, exomphalos, organomegaly, and characteristic groove on ear lobe along with other anomalies. These babies are prone for hypoglycaemia and Wilms' tumor.

Cerebral gigantism (Sotos syndrome) is of unknown etiology, characterized by large body size, large hands/feet, macrognathia, and mental retardation.

Clinically, most LFDs are asymptomatic except their size and features of causative disease, if present. However, even the constitutional LFDs are prone for: (a) obstructed labor, (b) hypoglycemia, and (c) polycythemia.

Management includes close monitoring of hematocrit and blood glucose levels during first 72 hours, and regular feeding. Additional sugar/oil fortified EBM may be given to prevent hypoglycemia, polycythemia. Primary disease should be managed appropriately.

12.11.4 POST-MATURITY

Babies born *after 42 completed weeks of gestation* are termed post-mature, post-term or post-dated babies.

Generally, beyond the term-gestation, placenta cannot sustain adequate fetal growth and develops degenerative changes, leading to fetal hypoxia, distress, growth retardation and sometimes, death.

Etiology: Most cases are *idiopathic* and born to Primiparous mothers. Rare causes include fetal anencephaly (delayed labor induction) or chromosomal defects, e.g. *Seckel's syndrome*.

Clinically signs of post-maturity include:

- Long, thin and wasted appearance with low birth weight, due to fetal dysplasia.
- Lack of vernix caseosa with peeling of skin, long nails and deep sole creases at birth.
- Yellowish staining of skin, nails and umbilical cord, due to *in utero* passage of meconium.
- Complications, e.g. meconium aspiration syndrome, birth asphyxia are common.

Management of these babies includes close monitoring for fetal distress, management of birth asphyxia and meconium aspiration syndrome, and prevention of hypoglycemia by early feeding. Application of oil on skin prevents it from peeling and dryness.

12.12 THERMOREGULATION DISORDERS

Temperature regulation is the one of the most important aspect of neonatal care, even in normal newborns. Fetus, who enjoys an isothermic environment (37°C) *in utero*, is suddenly exposed to low environmental temperature at birth, leading to rapid drop in body temperature (~ 0.3°C/min) by all modes of heat loss: (a) *evaporation* of amniotic fluid, (b) *convection* due to wind movements, (c) *radiation* due to temperature gradient, and (d) *conduction* to substances in contact with skin, e.g. linens.

Normal thermoregulation: Sudden cooling of neonatal skin stimulates *cutaneous thermoreceptors*, which convey the information to heat regulation centers in *pre-optic anterior hypothalamus*. Efferents from these centers are mainly *sympathetic* (adrenergic) in nature and stimulate various mechanisms for heat conservation and production, as follows:

- *Heat conservation* by peripheral vasoconstriction;
- *Heat production* by increased muscular activity, e.g. crying, limb movements, etc. Shivering mechanisms are not mature in newborns.
- *Heat production* by metabolic thermogenesis.

Metabolic thermogenesis is the predominant mode of heat production in newborns, which involves oxidation of metabolic fuels (brown fat) in presence of glucose and oxygen. *Brown fat* is a highly active metabolic substrate due to large number of mitochondria, predominantly present at the nape of neck, interscapular region, axilla, groin, and around kidneys and adrenals. In a FT-AGA baby, brown fat accounts for ~4% of body weight. Since most of it accumulates in last trimester, preterms have much lesser brown fat, and hence, more susceptible for hypothermia.

Thermoneutral environment: Human body can maintain its temperature only within a limited range, beyond which hypothermia or pyrexia results. However, maintenance of temperature even within this range requires constant metabolic activity, either to generate the heat or to increase evaporative heat loss, e.g. sweating.

Thermoneutral environment is *the narrow range of temperature at which baby can maintain its temperature with minimum metabolic activity and oxygen requirements*. It varies according to gestation, birth weight and postnatal age, ranging from ~33–31°C in full terms to ~35–33°C in VLBWs (higher value of the range is for first day of life and lower value is for 4th day onwards).

WHO recommends that neonatal temperature should be recorded in axilla once a day in apparently healthy term babies, thrice a day in healthy LBW (2–2.5 kg), 6-hourly in healthy VLBW <2 kg and every 2 hourly in sick newborns, using digital thermometer (mercury thermometers have been phased out). Low-reading rectal thermometer must be avoided due to risk of injury but may be used in sick, hypothermic babies with due care, gently inserted ~3 cm (2 cm in preterms) after greasing.

Rectal temperature represents body-core temperature, ~0.5–1.0°C higher than surface temperature.

Clinically too, temperature may be roughly assessed by touching the baby by the dorsum of hand on abdomen and hand/feet. Normal both abdomen and limbs should be warm. Warm abdomen and cold limbs indicate *"cold stress"* and cold abdomen and feet indicate *"Hypothermia"*.

Spectrum of temperature in newborns spans from *severe hypothermia* (<32°C) to *moderate hypothermia* (32–35.9°C), *cold stress* (36–36.4°C), *normal temperature* (36.4–37.4°C), *fever or hyperthermia* (37.5–38.5°C) and *hyperpyrexia* (>38.5°C).

12.12.1 HYPOTHERMIA

Hypothermia is more common and serious problem in newborns than fever or hyperthermia, defined as *skin temperature of <35.5°C or core temperature of <36°C*.

Etiology: Newborns are more susceptible to hypothermia than adults, due to—(a) disproportionately higher heat loss from larger surface area and lesser fat insulation, and (b) inadequate shivering thermogenesis. As metabolic thermogenesis is the only effective thermal defense in them, hypothermia is commonly seen in newborns with:

- Lack of brown fat, e.g. preterms and SFDs.
- Substrate deficiency, e.g. birth hypoxia, hypoglycemia.
- Circulatory insufficiency, e.g. infections and shock.
- Impaired central control, e.g. disorders affecting hypothalamus/neurological pathways.

In addition, cold exposure during procedures and transport, etc. further contributes to hypothermia in sick babies.

Pathogenesis: Prolonged hypothermia affects various metabolic activities **(Fig. 12.11)** leading to complications, e.g. (a) hypoglycemia, (b) cellular hypoxia, (c) metabolic acidosis, (d) septicemia due to impaired immune functions, and (e) poor weight gain due to diversion of metabolic substrates for heat production. In addition, impaired blood–brain barrier due to acidosis and other factors in hypothermia increases risk of kernicterus at relatively lower bilirubin levels.

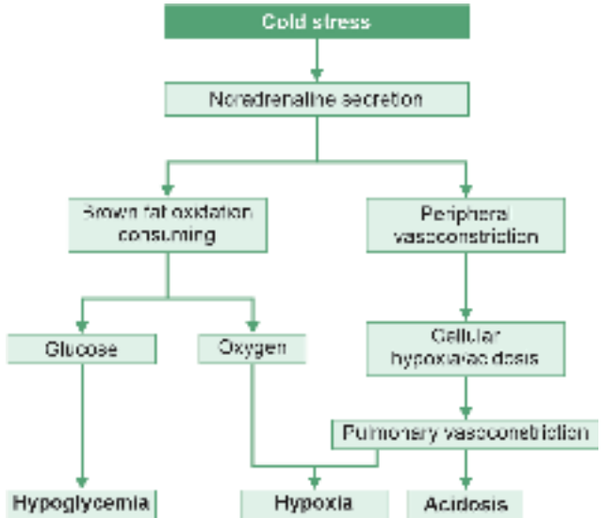


Fig. 12.11: Pathogenesis of hypothermia.

Clinical manifestations of hypothermia depends on its severity, including:

- *Changes in activity*, e.g. restlessness with excessive crying and body movements to generate heat in early cold stress, followed by sluggishness and inactivity.
- *Skin changes*, e.g. cold-clammy skin specially over limbs, followed by generalized mottling or pallor due to vasoconstriction and finally development of *sclerema*-characterized by hardening of skin, best appreciable over cheeks and shin of the tebia due to solidification of saturated fatty acids in subcutaneous tissue.
- *Depressed autonomic functions*, e.g. bradycardia, slow breathing and hypotension.

Diagnosis rests on digital/rectal temperature values. Simultaneous recording of axillary and core temperature with a *difference of >2°C indicates shock*.

Prevention of hypothermia is perhaps the most important step in neonatal care and includes:

- ***At birth***, by conducting the delivery in warm labor room (28–30°C), pre-warming of resuscitation area, receiving the baby on pre-warmed towels, wiping the baby well, wrapping in dry-warm linins and early breastfeeding to prevent hypoglycemia.
- ***In PNC wards*** by rooming-in with mother, keeping the room warm and baby covered, delayed bath till 24 hours and minimum handling. *Kangaroo mother care*, i.e. keeping the baby nestled inside the mother's cloths with close skin-to-skin contact is best method to provide warmth and prevent hypothermia in newborns, which also helps in promotion of breastfeeding and emotional bonding (Ch 12.12.2).
- ***In sick babies*** (NICU care) by—warm room, individual heat sources, e.g. incubators or radiant heat warmers, and minimum exposure during diagnostic and therapeutic procedures.
- ***During transport***, with use of transport incubators or thermocol boxes.

WHO, in 1997, recommended a set of inter-linked measures *(warm-chain)* during and soon after the delivery to minimize heat loss in newborns **(Table 12.31)**. Failure to implement any one of them will break the chain to put the baby at risk for hypothermia.

Management of hypothermic newborn includes:

- ***Gradual warming*** of baby in an incubator or warmer. Sudden warming may precipitate apneic spells and temperature gradient between baby's skin temperature

TABLE 12.31: Ten steps of warm chain (WHO 1997)
1. Warm delivery room
2. Immediate drying
3. Skin to skin contact
4. Breastfeeding
5. Bathing and weighing postponed
6. Appropriate clothing/bedding
7. Mother and baby together
8. Warm transportation
9. Warm resuscitation
10. Training and awareness raising

and environmental temperature should never exceed 1.5°C. However, severely hypothermic newborns may be warmed rapidly till skin temperature reaches 34°C, followed by slow warming.

- ***Continuous temperature monitoring*** by skin probes. Servo-control incubators or warmers are preferable, as they automatically adjust heater output according to baby's skin temperature.
- ***Substrate supplementation***, i.e. I/V Dextrose 10% (2 ml/kg bolus) and oxygen, to fulfil increased demand for metabolic thermogenesis. *IV hydrocortisone* (5 mg/kg 8 hourly for 3–5 days) may be used in cases of severe sclerema.
- ***Treatment of complications***, e.g. infections, hypoglycemia, acidosis, hypoxia, bleeding manifestations, etc.

Prognosis: Prolonged and severe hypothermia is associated with high mortality (25–50%). Sclerema and bleeding manifestations indicate poor prognosis.

12.12.2 KANGAROO MOTHER CARE

Kangaroo mother care (KMC) refers to a novel, low–cost intervention in care of the preterm or low birth weight infants, by nursing them in close skin-to-skin contact with mother or other caregiver, to promote temperature control, breastfeeding and emotional bonding, as well as to prevent hypothermia and infections.

First described by Dr Edgar Ray, Columbia, in 1978, the term derives its name from the similarities of marsupial baby care in Kangaroo species. KMC can be started at hospital and continued at home after discharge.

Benefits: Important benefits of KMC include: (a) reduced risk of hypothermia, (b) higher rates of exclusive breastfeeding, (c) better weight gain with early hospital discharge, (d) lesser morbidity in hospital and also post-discharge, (e) better emotional bonding between mother and baby, and (f) involvement of mother and family in neonatal care, reducing the stress associated with facility-care.

Prerequisites for successful KMC include birth weight <2500 gm and (a) baby should be hemodynamically stable*, (b) mother should be willing, with good health and hygiene, (c) support at the hospital as well as at home, (d) regular monitoring as well as post-discharge follow-up.

*KMC can be initiated in otherwise stable babies on IV fluids, tube feeding or oxygen. Most babies >1800 gm/>34 weeks can be directly managed with KMC; while lighter ones may need technology-based care in early days, till stable enough for KMC.

Procedure of KMC involves following steps:

Step I. Pre-KMC preparations including: (a) counseling the mother, spouse and other caregivers, (b) demonstration of actual procedure and answering their queries/apprehensions, (c) provision for appropriate, warm, front-open clothes for mother and baby; and (d) provision for suitable sitting arrangement, (e.g. reclining chairs) and adequate privacy.

Step II. Positioning of the mother–baby pair involves:

- Mother should be sitting or lying comfortably, preferably in semi-reclined posture;
- Baby's head should be placed between the mother's breasts in an upright position.
- Baby's head should be turned to one side in slightly extended position to ensure open airways and adequate eye to eye contact with mother.
- Baby's hips should be flexed and abducted in a "frog" position; the arms should also be flexed.
- Baby's abdomen should be at the level of the mother's epigastrium as maternal breathing stimulates the baby, reducing the risk of apnea.
- Baby's bottom should be supported with a sling/binder.
- Both mother and the baby should be properly covered as one unit **(Fig. 12.12)**.

Each skin-to-skin contact session should not last less than one hour to avoid frequent handling. Duration may be gradually increased up to 24 hours a day, interrupted only for changing diapers. Mother can eat and sleep in

Fig. 12.12: **Kangaroo mother care (KMC).**

KMC position, with proper support, preferably in semi-reclining position. KMC can be initiated in preterms within 24 hours of life (Early KMC) or even in babies on ventilators.

Monitoring: Babies during KMC should be closely monitored, specially in initial sittings, to ensure that: (a) neck is not too flexed/extended, (b) breathing is normal, and (c) feet and hands are warm. Mother should also be educated to watch for these parameters at home.

Feeding: KMC stimulates lactation and mother must be trained to feed the baby in KMC position. She must also be trained to express her milk and feed the baby by spoon, if required. Gavage feeding may continue during KMC, depending on the condition of baby.

When to stop KMC: Mother and baby may be discharged depending on their clinical status with adequate training and motivation to continue KMC at home, till it is comfortable and baby is not wriggling-out to show she/he is uncomfortable. Post-discharge, babies on KMC should be followed up till 37 weeks or 2500 gm weight, when KMC usually becomes unnecessary.

12.12.3 HYPERTHERMIA

Hyperthermia, i.e. core temperature exceeding 37.5°C, is of relatively lesser clinical significance in newborns, than older children.

Transient hyperthermia (overheating) is common in normal newborns due to ineffective mechanisms of heat loss, e.g. sweating, and should not be taken as indicator of underlying disease. *Sweating*—a most important mechanism to control fever in adults, is immature in newborns/infants <3 months.

Warmer care is a common cause of overheating in newborns, differentiated from true fever on the basis of—(a) normal appearance and activity, (b) pink skin (pale in fever), and (c) proportionately warm soles/palms with <2° difference between temperature at abdomen and hands (>3° in fever).

Persistent hyperthermia (fever) in newborns may be due to: (a) high environmental temperature, (b) infections (though hypothermia is more common), (c) dehydration, (d) CNS disorders, and (e) drugs, e.g. atropine derivatives.

Dehydration fever, lasting for 1–2 days, is a common problem in newborn during summer months due to poor fluid intake, specially in breastfed babies. However, baby remains alert and active despite fever. No treatment is needed, except monitoring for more serious causes.

12.13 RESPIRATORY DISORDERS IN NEWBORN

Respiratory functions in newborns are hampered by many *physiological handicaps*, e.g. (a) erratic central drive, (b) poor nasopharyngeal coordination, (c) excessively pliant airways and chest walls, (d) relative immaturity of surfactants, (e) cardiovascular transition at birth, and (f) higher oxygen requirements. Superimposed on these are other common and pathological problems, e.g. immature mechanical or immune defense mechanisms, congenital malformations and perinatal hypoxia.

12.13.1 D/D RESPIRATORY DISTRESS

Respiratory distress (RD) in newborn is a clinical diagnosis, defined as *tachypnea*, i.e. *(RR >60/min), associated with inspiratory intercostal retractions, expiratory grunt and cyanosis*.

Etiology: Intrauterine/postnatal pneumonia, meconium/milk aspiration, hyaline membrane disease (HMD) and congenital malformations are four major causes of RD in newborns, apart from other respiratory/extra-respiratory problems **(Table 12.32)**.

Diagnostic approach in neonatal RD includes:

I. Assessment of severity, based on
- *Signs of RD*, e.g. respiratory rate (RR), presence/severity of cyanosis, chest-wall retractions or grunt and air-entry on auscultation **(Table 12.33**, Downes' score).
- *Signs of hypoxia*, e.g. general activity, level of alertness, nature of cry, acceptance of feeds, etc., and
- *Laboratory indicators*, e.g. blood gas analysis.

TABLE 12.32: Causes of respiratory distress in newborns

Respiratory causes
- *Developmental:* HMD, TTN
- *Anatomical:* TOF, diaphragmatic hernia
- *Aspiration:*
  - Intrauterine (e.g. meconium)
  - Postnatal (e.g. milk)
- *Infections:* Intrauterine or postnatal pneumonia
- *Iatrogenic:* Pneumothorax, BPD
- *Others:* Wilson-Mikity syndrome

Extra-respiratory causes
- *Cardiac:* CHDs, myocarditis
- *Hematological:* Severe anemia, polycythemia
- *Neurological:* Birth asphyxia, diaphragmatic palsy
- *Metabolic:* Acidosis, inborn errors of metabolism

HMD: Hyaline membrane disease, **TTN:** Transient tachypnea of newborn, **TOF:** Tracheo-esophageal fistula, **BPD:** Bronchopulmonary dysplasia

TABLE 12.33: Clinical respiratory distress scoring

	Respiratory distress score		
Sign	***0***	***1***	***2***
RR	<60	60–80	>80/apnea
Cyanosis	Nil	At room air	At 40% O_2
Retractions	Nil	Mild	Moderate/severe
Grunting	Nil	Mild*	Loud
Air entry	Good	↓	Minimal

Interpretation: 0–4: Mild; 4–7: Moderate; >7: Severe
*audible only by stethoscope

TABLE 12.34: Causes of respiratory distress and age of onset

At birth or within 24 hours
- Meconium aspiration syndrome
- Transient tachypnea in newborn
- Hyaline membrane disease
- Birth asphyxia
- Intrauterine pneumonia
- Congenital airway obstruction or lung aplasia
- CNS trauma or malformations

Between 1st–7th day
- Postnatal aspiration
- Neonatal sepsis/pneumonia
- CHDs and CCF
- Iatrogenic—pneumothorax, acidosis

After first week
- Neonatal sepsis/pneumonia
- CHDs and CCF
- *Others:* Bronchopulmonary dysplasia, Wilson-Mikity syndrome

II. Etiological diagnosis depends on:
- *Gestational age:* HMD is an exclusive problem of preterms, while meconium aspiration syndrome (MAS) and transient tachypnea of newborn (TTN) are mostly seen in term babies.
- *Age of the onset* is a useful indicator of probable pathology for RD **(Table 12.34)**.
- *History of antenatal problems*, e.g. maternal diabetes (HMD), intrauterine infections (CHDs), polyhydramnios (tracheoesophageal fistula), oligohydramnios (lung aplasia), etc.
- *History of obstetric complications*, e.g. fetal distress (perinatal pneumonia), premature rupture of membranes (sepsis), meconium-stained delivery (MAS), cesarean delivery (TTN) low Apgar score (birth asphyxia) and neonatal resuscitation (pneumothorax), etc.
- *History of excessive frothing* from mouth on first day (tracheoesophageal fistula), choking/vomiting after feeds (postnatal aspiration).
- *Examination findings*, e.g. murmurs (CHDs), signs of sepsis (pneumonia), scaphoid abdomen (diaphragmatic hernia), etc.

III. Laboratory investigations depend on suspected cause, though following are necessary in all cases:
- X-ray chest
- *Sepsis screen*, e.g. CBC, PS and CRP levels
- Arterial blood gas analysis (ABG), in severe cases
- Tests for surfactant maturity (in preterms)

Other investigations, e.g. echocardiography for CHDs and metabolic screening for inborn errors are indicated in selected cases.

Management of RD depends on etiology, though general principles include:
- *Respiratory support* with humidified O_2 or assisted ventilation, as per clinical severity and ABG reports.
- *Supportive care,* i.e. adequate warmth, nutrition, fluid/electrolyte maintenance and prophylactic antibiotics. Parenteral nutrition is preferable in severe RD, due to risk of aspiration with oral feeds.
- *Continuous monitoring* by clinical assessment, non-invasive pulse oximetry and periodic ABGs.
- *Treatment of other complications*, e.g. hypoglycemia, acidosis, fluid/electrolyte imbalance, infections and anemia. Packed cell transfusion is indicated in babies with hematocrit <40, to improve oxygen-carrying capacity.
- *Treatment of primary cause*.

12.13.2 COMMON RESPIRATORY PROBLEMS

Some important causes of respiratory distress in newborns are as follows:

Hyaline membrane disease (HMD) is a common cause of respiratory morbidity/mortality in preterms, denoting *developmental immaturity of lung surfactant.* Surfactant deficiency leads to end-expiratory alveolar collapse and poor alveolar expansion on inspiration, with consequent decrease in lung compliance, complex ventilation-perfusion abnormalities and progressive respiratory failure.

Incidence of HMD is inversely related to gestational age. HMD may develop in 60–80% of preterms <28 weeks, 15–30% of preterms between 28 and 32 weeks and very rarely after 34 weeks. Incidence in Indian newborns is relatively less, probably due to high incidence of maternal infections that accelerate lung maturity.

Pathogenesis: Lack of the *surfactant*—a complex mixture of phospholipids and proteins that lines the inner surface of alveoli, is the core-pathology in HMD**.** Surfactant is secreted by alveolar type II pneumocytes from ~20th week onwards in increasing quantity, specially in last trimester. Main function of this surfactant is to prevent complete alveolar collapse during expiration and facilitate their expansion on next inspiration.

Surfactant deficiency is mostly developmental, in preterms. Other uncommon causes include—(a) delayed maturity in infants of diabetic mothers, and (b) destruction of type II alveolar cells due to perinatal complications, e.g. birth asphyxia, acidosis, hypothermia, Rh hemolytic disease and shock.

Surfactant deficiency means more negative pressure is required during inspiration to expand the collapsed alveoli of fetal lung. Inability of the highly compliant chest wall in preterms to generate enough negative inspiratory pressure leads to progressive alveolar atelectasis and hypoxia.

Diffuse atelectasis and hypoxia/acidosis-led vasoconstriction elevate pulmonary vascular pressure, leading to pulmonary hypertension > right to left shunt through PDA > ventilation-perfusion mismatch with increased alveolar:arterial oxygen gradient; and ultimately, respiratory failure **(Fig. 12.13)**.

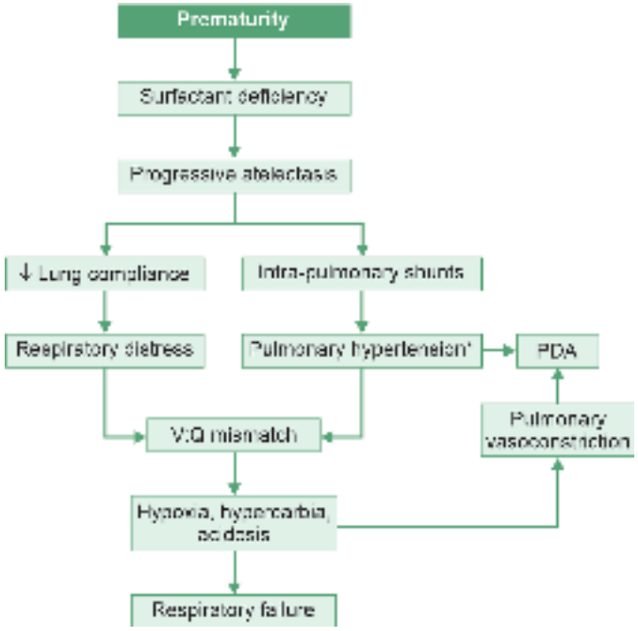


Fig. 12.13: Pathogenesis of HMD.
*Pulmonary hypertension > ↑ Rt ventricular pressure > PDA with Rt>Lt shunt

Autopsy findings in HMD reveal—(a) poorly expanded lungs, which do not float on water, (b) diffuse atelectesis, and (c) characteristic hyaline membrane on inner alveolar surfaces.

Clinical manifestations: HMD presents with progressive RD *since birth*, with—(a) tachypnea, (b) inspiratory chest-wall retractions, (c) expiratory grunt due to partially closed glottis—a protective mechanism to prevent end-expiratory alveolar collapse, and (d) cyanosis. Auscultatory findings are non-specific, with diminished breath sounds and fine inspiratory rales.

Untreated cases rapidly progress to respiratory failure in next 2–3 days, complicated with acidosis, hypotension, hypothermia and hypoglycemia.

Diagnosis of HMD should be considered in any preterm with progressive RD since birth, confirmed by:

- ***Chest X-rays:*** Radiological picture changes during the course of disease with (a) characteristic *fine reticular granularity with air bronchogram, (b) complete white-out appearance in severe disease* due to collapsed lungs, and (c) late *complications*, e.g. hyperinflation or pneumothorax **(Fig. 12.14)**.
- ***Surfactant maturity tests*** by—(i) shake test, (ii) biochemical tests, e.g. Lecithin-sphingomyelin ratio (L:S > 2 indicates adequate maturity).
  Shake test is a simple and bedside qualitative test to detect surfactant activity in amniotic fluid (antenatal prediction) or gastric juice (postnatal diagnosis). Add 0.5 ml of amniotic fluid/gastric aspirate in a mixture of normal saline (0.5 ml) and 95% ethyl alcohol (1.0 ml). Shake the mixture vigorously for 15 seconds and allow to stand it for 15 minutes. Presence of a rim of bubbles over >2/3rd of top liquid circumference indicates adequate surfactant activity. This test is false-positive if blood/meconium is present in test sample.
- ***Blood gas abnormalities*** are characterized by progressive hypoxemia, hypercarbia and metabolic acidosis.

Fig. 12.14: Hyaline membrane disease: White-out appearance with airbronchogram.

Prevention: Avoidance of prematurity is the most important prevention against HMD, though in unavoidable cases, following steps are necessary:

a. ***Postpone elective preterm labor*** as long as possible and assess surfactant maturity by amniotic fluid shake test or L:S ratio, before the induction.

b. ***Antenatal steroids*** to mother, if preterm labor is inevitable before 34 weeks, as total four doses IM dexamethasone 6 mg 12-hourly for our doses at least 24 hours before delivery is highly effective to accelerate surfactant maturity. Efficacy is maximum when baby delivers within 24 hours to 7 days after steroid and same course may repeated once (only) after 7–14 days if baby has not yet delivered and gestation is still < 34 weeks.

c. ***Prophylactic surfactant therapy*** at birth. However, early use of CPAP in delivery room is as effective as prophylactic surfactant therapy to prevent HMD.

Management of HMD aims to: (a) ensure adequate gaseous exchange in the lungs, (b) prevent further alveolar collapse and facilitate their expansion, (c) increase lung surfactant activity, (d) correct hemodynamic/metabolic abnormalities, and (e) manage secondary complications, i.e. infections, pneumothorax, etc.

All suspected HMDs must be managed in NICU with appropriate ventilatory support. Important steps include:

i. ***Initial stabilization*** with: (a) oxygen supplementation, (b) thermoregulation, (c) fluid/electrolyte correction,

(d) blood transfusion (if Hct <40) to improve oxygen carrying capacity, (e) treatment of complications, e.g. hypoglycemia, metabolic acidosis and infections, and (f) continuous monitoring.

ii. ***Ventilatory support*** is essential in most cases, though the mode of ventilation is guided by clinical severity, blood gas reports, and patient's breathing efforts.

Continuous positive airway pressure ventilation (CPAP) at a continuous distending pressure of 5–8 cm H_2O, is the ventilation of choice in HMD, indicated in cases with *PaO_2 <50 mm Hg despite 60% FiO_2 and able to breath spontaneously*. CPAP prevents complete collapse of alveoli at the end of expiration and thus facilitates longer gaseous exchange and easier re-expansion during inspiration. A recent meta-analysis suggests that non-invasive positive pressure ventilation (NIPPV) is superior to biphasic positive airway pressure (BiPAP) or CPAP ventilation to reduce the need of mechanical ventilation.

Assisted mechanical ventilation is indicated in babies with: (a) persistent ABG abnormalities despite 100% oxygen and CPAP or (b) no spontaneous respiration. Positive end-expiratory ventilation (PEEP) is indicated in these cases for the same reason as for CPAP in spontaneously breathing baby.

Mechanical ventilation must aim to keep PaO_2 50–70 mm Hg, $PaCO_2$ 45–65 mm Hg and pH 7.20–7.35, to ensure adequate ventilation without the risk of lung injury or oxygen toxicity. Recommended range of SaO_2 is 91–95%. At the time of weaning from ventilator, it is preferable to shift on nasal CPAP, followed by humidified high-flow oxygen (2–8 L/min) by nasal cannula.

iii. ***Surfactant replacement therapy (SRT)*** has revolutionized the prevention and treatment of HMD. Currently, two types of surfactants are available—biologically derived and recombinant preparations, former being more effective due to presence of surfactant proteins A and B.

SRT is complementary to CPAP and must be started as early rescue therapy within 2 hours of delivery in extreme preterms who require intubation in labour room or or later in babies on CPAP with FiO_2 requirements of > 40%.

Irrespective of the type, 100 mg/kg of surfactant, is instilled endotracheally via a catheter. After each 1–2 ml dose, infant must be given continuous positive pressure ventilation before next aliquot till full dose is administered. Surfactant can be administered by either *intubation-surfactant-extubate (INSURE)* technique or *less invasive surfactant administration (LISA)*.

Effective surfactant therapy is associated with rapid clinical improvement and correction of blood gas abnormalities. Rescue therapy is most effective when started within 24 hours of birth and usually 2–4 doses may be required at 6–12-hour interval. Pulmonary hemorrhage is the most important complications of surfactant therapy, apart from hypotension.

iv. ***Closure of PDA:*** Raised pulmonary pressure due to collapse alveoli and hypoxia-induced pulmonary arteriolar constriction in HMD leads to significant right-to-left shunting though PDA, which accentuates hypoxia. Pharmacological closure of ductus is indicated with 3 doses of either IV Indomethacin (0.2 mg/kg at 0,12 and 24 hours or Ibuprofen as 10 mg/kg (loading), followed by 5 mg/kg after 12 and 24 hours) However, currently IV Paracetamol 15 mg/kg 6-hourly is the preferred choice for closure of hemodynamically significant PDA. Prophylactic intervention is not indicated.

Outcome: Although most untreated cases of HMD are fatal, appropriate surfactant and ventilation therapy has reduced the mortality to ~10% in best centers. However, late complications, e.g. bronchopulmonary dysplasia or retinopathy of prematurity due to oxygen toxicity, are common in survivors.

Meconium aspiration syndrome (MAS): Intrauterine passage of meconium in amniotic fluid is an indicator of fetal distress and meconium-stained amniotic fluid (MSAF) is present in ~10–20% of deliveries. Meconium is a strong mucosal irritant. Babies born to MSAF deliveries are likely to aspirate it during first breath and develop meconium aspiration syndrome (MAS). However, only 5–10% of MSAF deliveries develop MAS, specially in term babies with thick meconium. .

Pathophysiology of MAS involves:

- *Airway obstruction* by aspirated meconium, leading to distal atelectasis (complete obstruction) or emphysema (partial ball-valve mechanism).
- *Chemical pneumonitis* due to constituents of meconium and release of inflammatory mediators (cytokines).
- *Surfactant injury* due to cytotoxic effects of meconium on alveolar type II cells.
- *Pulmonary hypertension* (PPHN) due to pulmonary vasoconstriction, and
- *Secondary infection*.

Clinically, MAS is more common in *term babies (rare in preterms)* and presents with progressive RD after 4–6 hours of birth. Chest may be hyperinflated with variable clinical signs in initial few hours, followed by signs of secondary bacterial pneumonia. MSAF babies often have external signs of meconium staining, e.g. greenish yellow staining of skin, nails and umbilical cord.

Diagnosis rests on history of MSAF delivery and development of respiratory distress after 4–6 hours in a term baby. Chest X-ray in suspected MAS should be delayed for 4–6 hours, to allow the radiological signs to

Fig. 12.15: **Meconium aspiration syndrome: Perihilar coarse opacities**

develop, which include: (a) bilateral perihilar/diffuse coarse opacities, (b) patchy emphysema/atelectasis, (c) pneumothorax (20–40%), and (d) consolidation due to super-infection **(Fig. 12.15)**.

Prevention: As per recent Neonatal resuscitation program (NRP) guidelines, resuscitation for a MSAF newborn must be on same protocols as for others and previously practiced interventions, e.g. endotracheal suction in non-vigorous babies or avoidance of positive pressure ventilation, are no longer recommended.

Management: All babies born to MSAF deliveries should be X-rayed after 6 hours of birth and observed for RD till 24 hours. In established MAS, treatment is largely supportive including: (a) oxygen or ventilatory assistance, (b) antibiotics to prevent/treat secondary infections, (c) chest physiotherapy, and (d) supportive measures including continuous monitoring. Mechanical ventilation is indicated in cases with severe hypoxemia (PaO_2 < 50 mm Hg) and hypercarbia ($PaCO_2$ > 60 mm Hg). *Steroids are contraindicated and may flare-up the bacterial pneumonitis.*

Other options, e.g. Sildenafil or Nitric oxoid therapy may be considered in cases with persistent pulmonary hypertension in newborn (PPHN).

Outcome: While mild cases may improve in 2–3 days, mortality is very high (>20–30%) in severe cases. Pneumothorax is most common complication. Survivors have higher risk of developing asthma in later life.

Perinatal pneumonia is the commonest cause of neonatal respiratory distress in India (>50%), which may be intrauterine or postnatal in origin.

Intrauterine pneumonia is more common in *term or post-term babies* due to higher risk of fetal distress and aspiration of amniotic contents.

Important *risk factors* include: (a) intrauterine infections, (b) premature rupture of membranes, (c) foul-smelling liquor amnii, (d) prolonged/obstructed labor, and (e) repeated vaginal examinations.

Infection is acquired either *in utero* by aspiration of infected amniotic fluid or during the passage through infected birth canal. Vaginal pathogens, e.g. *E. coli*, enterococci, Group B streptococci (rare in India), *Listeria monocytogenes* and Chlamydia are common causes of intrauterine pneumonia. Most cases manifest in first 3 days of life, except Chlamydia infections, which present as interstitial pneumonia in 2nd–3rd week.

Postnatal pneumonia is more common in *preterms or sick newborns* with following *predisposing factors:* (a) postnatal aspiration, (b) history of resuscitation, (c) cardio-respiratory problems, (d) surgical/intensive care (nosocomial infections).

Infection is acquired on post-natal aspiration or hematogenously from other septic sites. Nosocomial organisms, e.g. Klebsiella, Pseudomonas and staphylococci are predominant pathogens in these cases.

Diagnosis of perinatal pneumonia depends on clinic-radiological findings along with cultures from maternal genital tract and neonatal throat swab, gastric aspirate and blood. There is a good correlation between vaginal and neonatal pathogens in intrauterine pneumonia.

Treatment is guided by local antibiotic policy, preferably, an aminoglycoside with ampicillin/cloxacillin/cephalosporin, along with supportive care including ventilator assistance, if required.

Transient tachypnea in newborn (TTN) is a common, *self-limiting* cause of RD in *full-term* babies, born to cesarean or precipitate deliveries. *In utero*, lungs are filled with alveolar fluid, which is squeezed-out during vaginal passage due to external pressure. Lack of such pressure in LSCS or precipitate births, delays clearance of this fluid leading to TTN.

Clinically, these cases present with tachypnea since birth but without other signs of respiratory distress, e.g. intercostals recessions, cyanosis, etc. and baby is typically alert and active. Tachypnea usually subsides after 48–72 hours, with absorption of lung fluids via lymphatics.

Diagnosis rests on exclusion of other causes for RD. Chest X-ray may be normal or shows hyperinflated lungs with perihilar streaking due to dilated lymphatics and prominent interlobar fissure.

Management: TTN is self-limiting and no treatment is necessary except oxygen supplement, till tachypnea resolves.

Postnatal aspiration pneumonia is common in newborns with structural/functional oropharyngeal abnormalities, e.g. preterms, cleft palate, tracheoesophageal fistula and gastroesophageal reflux.

Clinically, these cases present at any postnatal age with history of sudden choking or vomiting, followed by dyspnea and cyanosis. Localized crepts may be present.

Diagnosis: Presence of milk in trachea on endotracheal intubation confirms the diagnosis. Chest X-ray shows parahilar streaking in early stages and diffuse/localized bronchopneumonia after super-infection.

Treatment is largely supportive, with prophylactic antibiotics.

Pneumothorax in newborns may be due to: (a) high pressure bag/mask resuscitation or mechanical ventilation, (b) staphylococcal pneumonia, (c) meconium aspiration, and (d) rupture of a congenital emphysematous bullae (*spontaneous pneumothorax).*

Clinically, pneumothorax should be suspected in any sick/ventilated child with sudden onset/deterioration of RD and blood gas abnormalities. X-ray chest is diagnostic. Transillumination of the chest on affected side using a fiber-optic probe might add to diagnosis.

Treatment includes emergency intercostal drainage in large *or* progressive pneumothorax, along with antibiotics and supportive care.

Pleural effusion in newborns may be due to: (a) chylothorax due to congenital/traumatic pathology of thoracic duct, (b) staphylococcal pneumonia, and (c) hydrops fetalis.

Chylothorax is more common on right side, filled initially with colorless fluid that turns to milky-white appearance, after a few days of feeding. Most cases recover spontaneously, though they should be fed on medium-chain triglycerides to reduce chyle production.

Persistent pulmonary hypertension in newborn (PPHN) or persistent fetal circulation (PFC) is a common hemodynamic complication in sick newborns, characterized by pulmonary vasospasm or hyperplasia leading to pulmonary hypertension and consequent right to left shunting through foramen ovale or PDA.

Clinically, PPHN is commonly seen in critically sick newborns with birth asphyxia, meconium aspiration, sepsis, acidosis, and hypoglycemia; and presents with persistent cyanosis and respiratory distress, despite adequate treatment of primary illness.

Diagnosis is confirmed by presence of a PaO_2 gradient between pre-ductal (right arm) and post-ductal (lower limb) arterial blood samples and/or on echocardiography. Chest skiagram may be normal.

Management includes—(a) correction of primary disease and complications, e.g. acidosis, (b) assisted ventilation, and (c) pulmonary vasodilators, e.g. Sildenafil, tolazoline, prostaglandins and dopamine. Nitric oxide inhalation (20 ppm) for 3–5 days to relax vascular smooth muscles may reduce the need for extra-corporeal membrane oxygenation (ECMO) which may be life-saving.

Diaphragmatic paralysis due to birth injury in large size babies with breech delivery is more common on right side, frequently associated with Erb's palsy. These cases may be asymptomatic or present with RD and paradoxical respiration. Diagnosis rests on paradoxical diaphragmatic movements on fluoroscopy. These cases must be differentiated from eventration, which is usually on left side, without paradoxical movements or Erb's palsy.

Bronchopulmonary dysplasia (BPD) is a chronic pulmonary complication of prolonged assisted ventilation, due to the combined effect of: (a) oxygen toxicity, (b) ventilator barotrauma, and (c) PDA. Incidence of BPD is inversely related to the gestational age. Most cases present with difficulty in weaning from ventilator/oxygen, after control of primary disease. Chest X-ray shows progressive nodular opacities with diffuse hyperinflation.

Severity of BPD is classified at the time of assessment on discharge or at 28 days (28–56 days in preterms <32 weeks), as *mild* (breathing at room air), *moderate* (need <30% oxygen) or *severe* (need >30% oxygen or positive pressure ventilation).

Specific treatment is not established, though diuretics, bronchodilators and a short course of steroids may allow these cases to wean from ventilator/oxygen. Recurrent chest infections and wheeze is common in survivors and ~1/3rd of them die in early infancy.

Neonatal stridor indicates inspiratory obstruction, usually due to: (a) developmental laryngomalacia, (b) luminal obstruction due to mucus, meconium or postintubation edema, (c) congenital anomalies, e.g. laryngotracheal webs, stenosis or cysts, (d) vocal cord palsy, and (e) external airway compression by vascular rings or cervical tumors.

Laryngomalacia is the commonest cause of persistent stridor, due to developmental flaccidity of laryngeal structures. Stridor is more prominent in supine position and typically reduces in prone position. Baby is otherwise comfortable without RD and feeds adequately.

Diagnosis rests on typical effect of posture on intensity of stridor and exclusion of other causes. No treatment is necessary except nursing in prone position and stridor gradually disappears after 4–6 months.

Neonatal apnea: Transient cessation of respiration without cyanosis or bradycardia is common in ~30–40% preterms, termed as *periodic breathing*, with no pathological consequence.

Apnea is defined as *sudden cessation of breathing for >20 seconds or of any duration associated with cyanosis and bradycardia,* which may lead to significant hypoxia and neurological damage.

Etiology: Recurrent apnea indicates gestational immaturity (*apnea of prematurity*) or a serious underlying disease

TABLE 12.35: Causes of recurrent apnea in newborn

- Apnea of prematurity (<32 weeks/1500 gm)
- Hyperthermia/hypothermia
- Neonatal septicemia
- *CNS:* Seizures, hypoxic-ischemic encephalopathy
- *Metabolic:* Hypoglycemia, dehydration
- *Respiratory:* Milk aspiration, RDS
- *Hematological:* Severe anemia
- *Drugs:* Maternal sedation
- *Others:* Painful stimuli, e.g. suction

(Table 12.35). Apnea, though not necessarily recurrent, may also develop due to (a) central causes, e.g. excessive sedation, (b) airway obstruction, e.g. neck-flexion or secretions. Aspiration is common even in term babies due to airway obstruction, e.g. milk aspiration or a reflex reaction to painful stimuli, e.g. suction.

Pathophysiology: Recurrent apnea of prematurity typically develops 2nd to 5th day and indicates immaturity of medullary centers to sustain adequate respiratory drive, due to poor afferent responsiveness *or* neurotransmitters insufficiency. Apnea within 24 hours of birth or after 5th day is more likely to be secondary.

Diagnosis: Recurrent apnea, except in extreme preterms, needs exclusion of serious underlying causes as well as environmental factors, e.g. hyperthermia.

Management: Apart from treatment of identified cause, specific management of apnea includes:

- ***During the attack:*** (i) airway suction, (ii) gentle physical stimulation, (iii) 100% oxygen to correct cerebral hypoxia, and (iv) positive pressure ventilation, if not responding to stimulation.
- ***Prevention of further attacks*** by: (i) avoidance of hyper/hypothermia and reflex apnea, (ii) continuous 40% oxygen supplementation or low pressure CPAP, (iii) drug therapy, and (iv) mechanical ventilation, if necessary.

Drug therapy for recurrent apnea includes IV Caffeine citrate 20 mg/kg loading followed by 5–7.5 mg/kg every 24 hours till 34 weeks of gestation or seven days post-weaning off respiratory support, whichever is later.

Surgical disorders, e.g. tracheoesophageal fistula, diaphragmatic hernia, etc. are important causes of respiratory distress on first day of life, discussed in Ch 14.6 and 14.7.

12.14 NEONATAL JAUNDICE

Jaundice is a common cause of parental concern in newborns, though most cases are benign and transient, due to developmental immaturity in bilirubin metabolism (*physiological jaundice*) rather than a pathological disease. However, it is essential to differentiate physiological from pathological jaundice, as in the later case, bilirubin levels may rise to dangerously high levels and cause neurological damage or *Kernicterus*.

Normal bilirubin metabolism may be divided into following steps:

a. ***Bilirubin production:*** About 3/4th of the bilirubin is derived from the breakdown of hemoglobin in reticuloendothelial system, while rest comes from myoglobin or heme-containing enzymes. One gram of hemoglobin produces 34 mg of bilirubin.

b. ***Transportation to liver:*** After production, bilirubin is transported to liver, mostly bound with albumin and partly as free bilirubin. The albumin-bind bilirubin cannot cross the blood–brain barrier (BBB) and hence, not neurotoxic. However, free unconjugated bilirubin is fat-soluble and readily crosses the BBB with potential risk of kernicterus.

c. ***Hepatic conjugation:*** In liver, bilirubin dissociates from albumin to enter hepatocytes and combines with *Ligandin* (Y-protein) to reach the site of conjugation, i.e. *endoplasmic reticulum*. Here, it conjugates with glucuronic acid in presence of an enzyme *Uridine diphosphate glucoronyl transferase* (UDPGT), to form mono-/di-glucuronides, i.e. *conjugated bilirubin*. Unlike unconjugated bilirubin, conjugated bilirubin is water soluble and cannot cross BBB (non-neurotoxic).

d. ***Excretion of conjugated bilirubin:*** Conjugated bilirubin is excreted in bile to reach the intestines, where part of it is further metabolized for excretion as *stercobilinogen* in stools and *urobilinogen* in urine. Normal gut flora is essential for conversion of conjugated bilirubin into stercobilinogen/urobilinogen.

e. ***Enterohepatic circulation:*** Part of the conjugated bilirubin excreted in gut, reverts back to unconjugated form by enzyme β-*glucuronidase* and re-absorbed again for liver metabolism.

12.14.1 PHYSIOLOGICAL JAUNDICE

Physiological jaundice is a sign of developmental immaturity in bilirubin metabolism, seen in >50% of Term newborns and >80% of preterms.

Cardinal features of physiological jaundice are:

- Onset beyond 24 hours of birth (N: 48–72 hours)
- Maximum intensity on 4th day (5/6th day in preterms)
- Maximum. Serum bilirubin <12 mg/dl (<15 in preterms)
- Disappears by 10th day (14th day in preterms)
- Active newborn without other problems

Etiophysiology: Physiological jaundice indicates various developmental immaturities in newborns, as follows:

- *Increased bilirubin production*, ~3 times higher than in adults, due to higher hemoglobin content and shorter lifespan of fetal RBCs (90 days).
- *Developmental hepatic immaturity* with relative deficiency of *Ligandin* for bilirubin transport within hepatocytes and UDPGT for conjugation.

- *Underdeveloped gut flora*, with inadequate conversion of conjugated bilirubin into excretable pigments-stercobilinogen and urobilinogen. Consequent delay in bilirubin excretion facilitates entero-hepatic circulation.
- *Increased enterohepatic circulation* due to high β-glucoronidase activity in gut, especially when feeding is delayed. Early feeding promotes development of normal flora, which destroys this enzyme and limits enterohepatic circulation.

These physiological handicaps are more pronounced in preterm, LBW and sick newborns, e.g. hypoglycemia, asphyxia, etc., leading to *exaggerated physiological jaundice.*

Diagnosis of physiological jaundice rests on cardinal features (as above) and exclusion of pathological causes.

Management: No specific treatment is needed in physiological jaundice, except—(a) proper feeding, (b) prevention of hypothermia, and (c) clinical monitoring and follow-up after 10–14 days to confirm disappearance of jaundice. However, cases with exaggerated physiological jaundice need to be treated as pathological jaundice.

12.14.2 DIAGNOSTIC APPROACH IN NEONATAL JAUNDICE

Neonatal jaundice may be physiological or pathological due to many causes **(Table 12.36)**. Diagnostic approach in these cases aims to answer following questions:

Step I. Whether it is pathological? Neonatal jaundice is considered as pathological in presence of any of the following features:

- Appears within 24 hours of birth,
- S. bilirubin >12 mg/dl (>15 in preterm)
- Persistence of icterus > 10th day (>14th day in preterm),
- Sick child, e.g. vomiting, lethargy, poor feeding, apnoea, hypothermia, etc.

All suspected cases of pathological jaundice require detailed investigation to identify the cause, constant monitoring and timely therapeutic interventions.

Step II. Whether it is predominantly unconjugated or conjugated? Pathological jaundice may be broadly divided in: (a) *unconjugated or* indirect, or (b) *conjugated* or direct hyperbilirubinemia. Conjugated hyperbilirubinemia is relatively less common and usually manifests beyond 2nd week of life with progressive icterus and typical *clay-color* stools.

Step III. What is the precise cause? Hemolytic disease of newborn (Rh/ABO incompatibility), septicemia and congenital haemolytic anemia are three leading causes of unconjugated jaundice, while conjugated jaundice usually indicates extrahepatic biliary atresia (EHBA) or neonatal hepatitis. However, other causes **(Table 12.40)** should be excluded

Step IV. What is the severity? While serial bilirubin level is the best indicator for severity in neonatal jaundice,

TABLE 12.36: Causes of neonatal jaundice

- **Physiological**
- **Pathological (predominantly unconjugated)**
  - ***Overproduction of bilirubin***
    - *Hemolytic disease of newborn (Rh/ABO)*
    - *Congenital hemolytic anemia:*
      - Membrane defects, e.g. H. spherocytosis
      - Enzyme defects, e.g. G6PD deficiency
      - Hemoglobinopathies, e.g. Thal. major
    - *Acquired hemolysis* due to
      - Polycythemia
      - Cephalohematoma
      - Intrauterine infections, septicemia
      - *Drugs:* Vitamin K, sulfonamides, etc.
  - ***Impaired hepatic metabolism***
    - *Inherited enzyme defects:*
      - *UDPGT deficiency:* Crigler-Najjar syndrome
      - Specific Y/Z protein (Ligandin) deficiency
      - *IEMs:* Galactosemia, Gilbert syndrome
    - *Inhibition of enzyme activity*
      - Breast-milk jaundice
      - Lucey-Driscoll syndrome
      - Drugs, e.g. chloramphenicol, aminoglycosides
    - *Endocrinal disorders:* Hypothyroidism
- **Pathological (predominantly conjugated)**
  - ***Impaired excretion (cholestasis syndromes)***
    - *Neonatal hepatitis*
      - Idiopathic neonatal hepatitis
      - Intrauterine infections
      - *Metabolic:* galactosemia, α_1 antitrypsin deficiency
    - *Biliary tract malformations*
      - Extra-hepatic biliary atresia (EHBA)
      - Intra-hepatic biliary atresia (IHBA)
      - Choledochal cysts
    - *Inspissated bile syndrome*
    - *Inherited:* Dubin-Johnson syndrome
  - ***Increased enterohepatic circulation***
    - *Intestinal stasis:* IHPS, meconium ileus
    - *Poor gut flora:* Delayed feeding, prolonged antibiotics

IHPS: Infantile hypertrophic pyloric stenosis

TABLE 12.37: Clinical assessment of the severity in neonatal jaundice (Cramer criteria)

Icterus visible on..	*Expected bilirubin levels*
Face	<5 (4–8 mg/dl)
Upper trunk	<8 (5–12 mg/dl)
Lower trunk	<10 (8–16 mg/dl)
Arms and legs	<15 (11–18 mg/dl)
Palm and soles	>15 mg/dl

Table 12.37 provides a commonly used "Kramer criteria" for clinical assessment of severity.

A diagnostic algorithm for neonatal jaundice is given in **Fig. 12.16**, though important diagnostic clues are as follows:

Clinical evaluation, with special reference to:

- Age of appearance **(Table 12.38)**

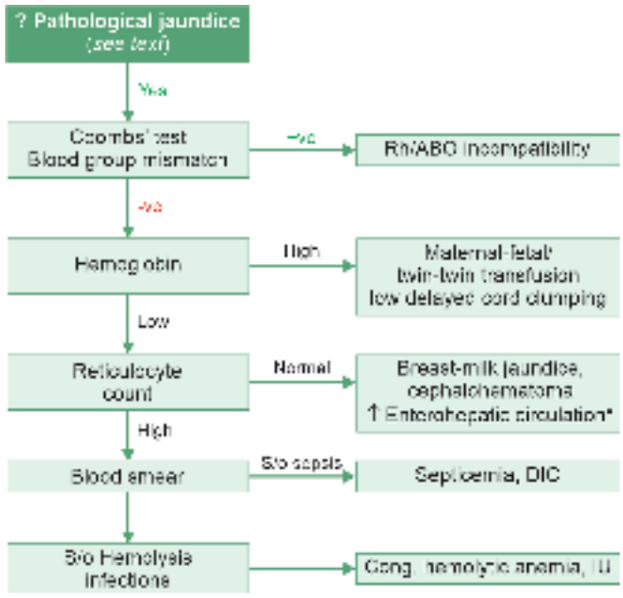


Fig. 12.16: Diagnostic algorithm for N. hyperbilirubinemia.
*For example, paralytic ileus, late feeding, intestinal obstruction

TABLE 12.38: Age of onset in neonatal jaundice

- **Within 24 hours of Birth**
  - Hemolytic disease of newborn (Rh/ABO)
  - Intrauterine infections
  - Cong. hemolytic anemia, e.g. thalassemia major
  - Maternal medications, e.g. Vit K, sulfonamides, etc.
  - Crigler-Najjar syndrome
- **Between 24 and 72 hours**
  - All of the above, plus
  - Physiological jaundice
  - Exaggerated physiological jaundice
  - Neonatal sepsis
- **Between 72 hours and 14th day**
  - All of the above, plus
  - Breast milk jaundice
  - Septicemia
  - Gut stasis/sterilization: IHPS, antibiotic therapy
- **Beyond 14th day of life**
  - Neonatal hepatitis (idiopathic, secondary)
  - Biliary atresia (EHBA/IHBA)

IHPS: Infantile hypertrophic pyeloric stenosis

- Duration of icterus: Persistent icterus > 2 weeks may be due to hypothyroidism, Crigler-Najjar syndrome, neonatal cholestasis disorders, or inspissated bile syndrome.
- Perinatal problems, e.g. preterm, asphyxia, sepsis.
- General appearance and activity level.
- Type of feeding (breast milk jaundice).
- Exposure to drugs causing hyperbilirubinemia

Laboratory evaluation include:

- *Baseline investigations* in all cases
  - Serum bilirubin levels (total and direct)
  - Blood grouping (ABO/Rh type)
  - *Hemolysis screen:* Hct, Hb and P. smear
  - *Sepsis screen:* TLC, band-cell count, CRP
- Investigations in indirect hyperbilirubinemia
  - Serological tests for intrauterine infections
  - Hb electrophoresis, osmotic fragility, G6PD estimation for congenital hemolytic anemia.
  - Metabolic screening for enzyme defects
- Investigations in direct hyperbilirubinemia
  - Hepatobiliary scan
  - Liver biopsy

12.14.3 UNCONJUGATED HYPERBILIRUBINEMIA

Unconjugated hyperbilirubinemia is a major cause of concern in early neonatal period, due to potential risk of neurotoxicity. Hemolytic disease of newborn (HDN) due to Rhesus or ABO blood group incompatibility is the commonest cause of severe unconjugated hyperbilirubinemia. Followed by breast milk jaundice and Crigler-Najjar syndrome, etc. Minor blood group incompatibilities, though probably more common, rarely produce significant hemolysis.

Rhesus hemolytic disease of newborn (Rh-HDN) is characterized by severe hemolysis of fetal RBCs in a Rh +ve fetus/newborn born to Rh-ve mother, due to transplacental transfer of maternal anti-D (anti-Rh) antibodies. In India, ~5% of mothers are Rh-negative. Rh blood group system is characterized by three antigens, i.e. C, D and E. Of these, D is the most important antigen and hence, anti-Rh antibodies are also commonly termed as anti-D antibodies.

Pathogenesis: There are no inborn anti-Rh antibodies in humans and production of anti-D antibodies in mother requires sensitization of her immune system by exposure to Rh +ve antigen. Usually, this sensitization occurs during first trimester by seepage of Rh+ve fetal RBCs to maternal side via immature placenta, which stimulates maternal anti-D IgG production. However, initial sensitization may also occur during previous deliveries, abortions/stillbirths or Rh +ve blood transfusions.

These antibodies, mainly of IgG class, cross the placental barrier to produce hemolysis of fetal RBCs Since the quantum of these antibodies depends on frequency of antigenic exposure, first babies are less affected than subsequent births.

Clinical spectrum of Rh-HDN varies from insignificant hemolysis to the severe hemolytic anemia in fetal life, leading to *hydrops fetalis* and stillbirth. *Severity tends to increase with increasing birth order.*

Erythroblastosis fetalis, the commonest presentation of Rh-HDN, manifest with two cardinal features: (a) moderate to severe hemolytic *anemia* at birth, and (b) appearance of *icterus* within first 24 hours. Untreated cases may rapidly progress to reach dangerously high

TABLE 12.39: Causes of hydrops fetalis

Immune hydrops: Hemolytic disease of newborn
Non-immune hydrops:
- *Severe anemia:* α-thalassemia, G6PD deficiency
- Renal malformations, e.g. agenesis, polycystic disease
- Pulmonary aplasia/hypoplasia
- *Intrauterine infections:* Syphilis, CMV
- *Chromosomal:* Down syndrome
- Placental AV malformations

bilirubin levels and consequent neurotoxicity, i.e. *kernicterus*. Other complications, e.g. hypoglycemia, CCF are common.

Hydrops fetalis: Most severe presentation, is characterized by—(a) severe anemia, (b) generalized anasarca with ascites/pleural effusion and (c) hepatosplenomegaly *at birth.* Most cases die *in utero* or soon after birth and must be differentiated from other causes of non-immune hydrops fetalis **(Table 12.39)**.

Diagnosis rests on Rh-group setting (Rh +ve baby born to Rh-ve mother), though the severity of hemolysis and extent of hyperbilirubinemia should be monitored both, antenatally as well as postnatally.

Antenatal assessment of severity is indicated in high-risk Rh-ve mothers with history of previous transfusions, abortions, stillbirths or Rh +ve delivery. This requires periodic estimation of maternal anti-D titers. Those with high titers need assessment of *optical density of amniotic fluid*, from 24th week onwards, every 2–3 weeks. An optical density difference of >0.1 from previous value *or* consistent rise on consecutive analysis, indicate severe hemolysis.

At the time of birth, cord blood should be collected in all babies of Rh–ve mothers, for grouping, Hb/Hct, direct Coombs' test and S.bilirubin levels. A positive direct Coombs' test confirms the diagnosis, though it may be false –ve, if sample is contaminated by Wharton's jelly.

Postnatally, symptomatic cases should be monitored by serial Hb, Hct and S. bilirubin levels, to decide the severity and further management. *Peripheral smear is another indicator of on-going hemolysis, showing reticulocytosis, normoblasts and other immature cells.*

Prevention of Rh-HDN involves:
- Pre-conceptional counseling with Rh-testing,
- Avoid mismatch transfusions in Rh –ve mothers,
- Anti-D immunoglobulins to mother within 72 hours of each delivery/abortion.

Although the dose of anti-D depends on the extent of expected feto-maternal leak, 250 mg is usually enough to protect against most cases with ~10 ml of feto-maternal hemorrhage.

Management of Rh-HDN aims to prevent: (a) severe anemia, and (b) bilirubin toxicity, e.g. kernicterus.
- ***Antenatal management*** of severe intrauterine HDN involves repeated fetal transfusions of 50 ml Rh-ve packed RBCs, via cordocentesis under USG guidance, till delivery.
- ***Postnatal management*** depends on the severity of hyperbilirubinemia, using two important interventions-phototherapy or exchange transfusion, discussed later in this chapter.

Apart from critical bilirubin levels **(Table 12.44)**, *early exchange transfusion* is also indicated in Rh-HDN with—(a) cord bilirubin >5 mg/dl, (b) Cord Hb <10 mg/dl, (c) bilirubin rise >1 mg/dl/hr despite phototherapy, and (d) S. bilirubin >20 mg/dl at any age.

Intravenous immunoglobulin (0.5–1.0 g/kg/dose; repeat in 12 hr) is a useful adjunctive therapy to phototherapy in Rh-HDN to reduce the need for exchange transfusion.

ABO-Hemolytic disease (ABO-HDN) is emerging as a major cause of neonatal hyperbilirubinemia after relative control of Rh-HDN by anti-D prophylaxis.

Pathogenesis: Isohemagglutinin IgG antibodies are nearly always present in mothers against the ABO antigen, which is absent on her own RBCs (Group 'O' mothers have both anti-A and B antibodies, while group 'A' and 'B' mothers have anti-B or anti-A antibodies respectively). When a fetus with different ABO group is conceived, these IgG antibodies cross placenta to cause hemolysis of fetal RBCs. However, as there is no active stimulation of maternal antibody production unlike Rh-HDN and only pre-formed antibodies are transferred, hemolysis is less severe. Although ABO incompatibility is present in >25% deliveries, only <10% manifest clinically.

Clinical manifestations are most severe in settings of 'O' mother and 'A' or 'B' baby. ABO-HDN is more common in females and more severe in first-born baby. *Unlike Rh-HDN, Severity of ABO-HDN tends to decrease in subsequent deliveries.* Jaundice usually appears after 24 hours, peaks less than in Rh-HDN and phototherapy is often enough, with less need for exchange transfusions.

Diagnosis depends on feto-maternal ABO mismatch and signs of hemolysis on peripheral smear. Direct Coombs' test is negative.

Management is same as for Rh-HDN or other causes of indirect hyperbilirubinemia, guided by serum bilirubin levels.

Breast milk jaundice is seen in ~2% of breastfed babies, who are otherwise healthy.

Etiology: Exact etiology of breast milk jaundice is unclear, though probably relates to: (a) Presence of *3–20β pregnanediol*, unsaturated fatty acids or unknown substances in human-milk, which inhibit hepatic conjugation; or (b) increased enterohepatic circulation, due to presence of β-*glucuronidase* in breast milk.

Clinically these newborns are otherwise *fullterm, healthy and active*. Jaundice develops during first week of lifelike

physiological jaundice but rather than disappearing by 7–10 day, it deepens gradually to peak by 2–3 weeks (max S. bilirubin as high as 10–30 mg/dl), followed by gradual reduction and disappearance by 3–12 weeks, even if breastfeeds are continued.

Diagnosis depends on exclusion of other causes and *typical* healthy, active baby, despite deep jaundice. In a suspected case, it may be confirmed by temporary stoppage of breastfeeds, which brings down the bilirubin levels rapidly with 48–72 hours. These levels may rise again on subsequent resumption of breastfeeding, albeit marginally and less than previous values.

Management: No specific management is required and breastfeeding should be continued even if bilirubin levels reach 20 mg/dl, though phototherapy may be necessary. Supplementing breastfeeds with top-feeds is not advisable, as mixed feeding is known to cause further rise in bilirubin.

Crigler-Najjar syndrome is an inherited enzyme defect, characterized by non-hemolytic unconjugated hyperbilirubinemia due to *Glucuronyl Transferase deficiency.*

- ***Type I** defect* (autosomal recessive), presents with rapidly progressive hyperbilirubinemia since birth and no response to phenobarbitone therapy.
- ***Type II** defect* (autosomal dominant) is a milder variant, which presents at any age with mild persistent icterus and unconjugated bilirubinemia. Family history is common. Unlike type I, These cases show rapid decline in bilirubin levels with oral phenobarbitone therapy (3–5 mg/kg/day).

Diagnosis should be considered in any case of unconjugated hyperbilirubinemia in newborn or infant, without evidence of hemolysis or infection. Enzyme estimation is diagnostic, though not easily available.

Management of type I disease is same as for other causes of unconjugated hyperbilirubinemia, i.e. phototherapy/exchange transfusion, depending on bilirubin levels. Type II disease may be controlled by long-term phenobarbitone therapy, with good prognosis.

Drug-induced jaundice in newborns may be caused by:

- Increased hemolysis and bilirubin production in G6PD deficiency (*antimalarials*),
- Displacement of conjugated bilirubin from binding sites (*sulphonamides, salicylates*),
- Competitive inhibition of Y-receptor proteins (*vitamin K*) or UDPGT (*aminoglycosides, chloramphenicol*),
- Damage to normal gut flora (*neomycin*).

Management of Unconjugated Hyperbilirubinemia

Management of unconjugated hyperbilirubinemia. Irrespective of the cause, primarily aims to keep free indirect bilirubin levels within the safe-limits of neurotoxicity, till spontaneous decline in hemolysis and maturity of liver functions. However, these *safe-limits* are not well-defined and depend on the gestational age, birth weight and co-existing problems that impair blood–brain barrier **(Table 12.45)**.

Important measures to facilitate bilirubin excretion or limit indirect hyperbilirubinemia include: (a) Phototherapy, (b) exchange transfusion, and (c) ancillary measures, discussed as follows:

I. Phototherapy is most widely used method to prevent/treat unconjugated hyperbilirubinemia and avert the need for exchange transfusion.

Principle: In phototherapy, an icteric newborn is exposed to a specific band of light frequency (425–475 nm) that leads to *photo-isomerization* of neurotoxic unconjugated bilirubin (present in skin) to non-toxic isomers, which are then excreted through normal channels. Phototherapy also reduces bilirubin levels by *photo-oxidation* as well as by enhancing *hepatic excretion* of unconjugated bilirubin into intestinal lumen.

Indications for phototherapy depends on total serum bilirubin (TSB) levels and the anticipated risk for neurotoxicity, which itself depends on the gestation, postnatal age and other risk factors **(Table 12.40)**.

American Academy of Pediatrics (2022) has recently updated separate cut-off for TSB levels in infants of different gestations 23 weeks onwards to initiate phototherapy, with or without neurotoxicity risk factors, i.e. presence of haemolytic disease, sepsis, low albumin levels <3 gm/dl, etc. and significant clinical instability in preceding 24 hours.

Procedure: Phototherapy is provided by prolonged exposure of baby to the specified frequency of photoemittance under an overhead *phototherapy unit*, usually using LED lamps at present. Important pre-requisites for effective phototherapy are:

- Light source should provide an irradiance of >30 µW/cm^2/nm within the 460–490 nm range, at the level of baby's skin (monitor with *flux meter)*. The source should also be covered with a perplex shield to cut-off harmful infra-red rays.
- Distance between baby and light source must be ~ 30–45 cm.
- Baby should be fully uncovered except eyes and genital region, to avoid radiation injury to sensitive organs. Double surface and triple surface phototherapy units are available with marginal benefits.
- Adequate breastfeeding is *must* to avoid dehydration due to insensible losses. Add 20% extra fluids to maintenance requirements, if baby is on IV fluids.
- Phototherapy is given continuously, except during BF, with intermittent bilirubin monitoring. *Intermittent Phototherapy* for 6–8 hours (with 2–3 hours gap) though

as effective as continuous phototherapy, carries potential risk of more DNA damage.
- Monitor body temperature every 2–4 hourly and TSB levels every 12–24 hours.
- Stop phototherapy only when two TSB values are below the cut-off point, though clinical monitoring should continue to check for rebound hyperbilirubinemia.

Exposure to sunlight is not an alternative to phototherapy and may be harmful due to prolonged exposure to UV rays.

Modifications to increase effectiveness of the PT include:
- *Double surface phototherapy* to expose front as well as back surface of the baby, allows faster reduction in bilirubin levels.
- *Intensive phototherapy*, i.e. lesser distance between light source and infant (15–20 cm), may be more effective.
- *Intermittent phototherapy* for 6–8 hours (with 2–3 hours gap) is as effective as continuous phototherapy, though with potential risk of more DNA damage.

Effectiveness of phototherapy depends on: (a) initial bilirubin levels, (b) surface area of exposed skin, (c) gestation/weight of baby, and (d) quality and distance from the light source. Although riboflavin supplements appear to increase its effectivity, it is not commonly used due to probable risk of DNA toxicity.

Complications: Although phototherapy is a safe and non-invasive intervention, following complications may develop in some cases:
- Dehydration due to insensible water loss,
- Loose-green stools due to bilirubin catabolites,
- Hypo/hyperthermia,
- Phototherapy rash,
- Bronze skin discoloration, if erroneously given to a case of conjugated hyperbilirubinemia, due to formation of an isomer - *bilifuscin*;
- Late effects due to cellular damage to eyes, genitals (sterility) and skin (cancers).

II. Exchange transfusion is the most effective method to reduce indirect bilirubin levels, indicated only in severe hyperbilirubinemia.

Principle: Exchange transfusion aims to: (a) remove partially hemolysed, antigen-coated RBCs as well as unattached antigen from recipient's circulation, (b) replace them by unsensitized donor's RBCs, and (c) reduce circulating bilirubin metabolites.

Indications for exchange transfusion include critical TSB levels **(Table 12.40)**, though pre-emptive exchange transfusion may also be considered if *cord bilirubin is > 5 mg/dl or rising at the rate of > 1 mg/dl/hour despite phototherapy*.

American Academy of Pediatrics (2022) has recently updated separate cut-off levels for total serum bilirubin in infants of different gestations 23 weeks onwards to consider exchange transfusion, with or without neurotoxicity risk factors.

TABLE 12.40: Cut-off unconjugated bilirubin levels for phototherapy and exchange transfusion (mg/dl)*

	Phototherapy	**Exchange**
Uncomplicated fullterms *(according to age)*		
<24 hours	Any	–
25–48 hours	12–15	20–25
49–72 hours	15–18	25–30
>72 hours	17–20	25–30
Preterms/sick fullterms** *(according to birth weight)*		
<1000 gm	Any	10–12
1000–1500 gm	7–9	12–15
1500–2000 gm	10–12	15–18
>2000 gm	13–15	18–20

*Lower values of range indicate *need to consider*, while higher value indicate *absolute need for intervention*.
**For example, asphyxia, sepsis, hypoglycemia

Exchange transfusion is also used for other indications, e.g. severe septicaemia, severe anemia with CCF and severe polycythemia (Hct >65) as well as to remove toxins in some cases of inborn errors of metabolism, e.g. hyperglycinemia.

Choice of Blood
- *Rh-HDN:* Rh-ve blood with ABO group of *baby*, *or* O-ve blood cross-matched with *mother and baby.*
- *ABO-HDN:* 'O' Rh specific (with low anti-A or B-titers)
- *Other indications:* ABO and Rh group of *baby*.

Volume of exchange: Usually double of the baby's blood volume (80 ml/kg) needs to be exchanged for effective results, which replaces >85% of baby's blood and brings down bilirubin levels to ~ 50% of pre-exchange values.

Route: Usually umbilical vein is cannulized for exchange transfusion due to its size, though peripheral veins may be used, if umbilical cannulation is not possible or umbilical sepsis is present. Normally, umbilical vein may be cannulized till 5–7 days.

Methodology: While detailed discussion is beyond the scope of this book, basic steps include:
- Obtain a free-flowing venous access and connect with a three-way cannula,
- Draw 10 cc of baby's blood for pre-exchange serum bilirubin and electrolyte levels.
- Withdraw 10–20 ml aliquot of baby's blood and then replace it with equal volume of donor's blood. Repeat the cycles till desired volume is exchanged.
- Monitor for complications. After each 50 ml exchange, 1 ml 10% calcium gluconate should be infused if ACD/CPD blood is used, to prevent bleeding tendency.
- Send last baby's blood sample at the end of exchange transfusion, for post-exchange bilirubin/electrolyte estimation.

Complications: Exchange transfusion needs expert hands and common complications include:

- *Metabolic:* Hypocalcemia, hypoglycemia, acidosis
- *Infections:* Umb. sepsis, peritonitis, septicemia, NEC
- *Traumatic:* Cord bleeding, catheter injury
- *Volume overload*
- *Hypothermia*
- *Late anemia*, due to shorter life-span of infused RBCs that necessitates top-up transfusion.

III. Ancillary measures: Following measures, though of limited efficacy, are useful adjunct to phototherapy/exchange transfusion in neonatal hyperbilirubinemia:

- *IV albumin* infusion (0.5 gm/kg) to bind free bilirubin, which is neurotoxic.
- *IV immunoglobulins* (0.5–1.0 gm/kg over 2–4 hours to reduce immune mediated hemolysis in Rh-HDN due to blocking the Fc receptors of reticuloendothelial cells which destroy antibody coated RBCs.
- *Adequate breastfeeding* to facilitate growth of gut flora.
- *PO bilirubin-binders*, e.g. agar, to prevent enterohepatic circulation.
- *Management of BBB impairing conditions*, e.g. hypoxia, acidosis and sepsis.
- *Avoidance of drugs*, known to displace bilirubin from albumin-binding sites, e.g. sulfa-drugs.
- Other modalities with equivocal results include use of phenobarbitone as microsomal enzyme inducer to enhance the conjugation of bilirubin, and synthetic metalloporphyrins to competitively inhibit heme oxygenase—a limiting enzyme for bilirubin synthesis. Use of oral bilirubin binders, e.g. agar, to prevent enterohepatic circulation is of limited value.

12.14.4 KERNICTERUS

Kernicterus is the rare but most severe complication of bilirubin toxicity in indirect hyperbilirubinenia, characterized by acute neurological signs mainly involving *extrapyramidal system*, with high mortality or long-term sequelae.

The term *"Bilirubin encephalopathy"* or *"Bilirubin-induced neurological dysfunction"* (BIND) is also used to encompass wider range of clinical presentations of bilirubin toxicity, including kernicterus.

Etiopathogenesis: Bilirubin is neurotoxic. However, following factors determine risk of kernicterus:

- *Severity of bilirubinemia:* Kernicterus develops only after a critical serum bilirubin level has reached.
- *Type of bilirubin:* Conjugated bilirubin is not neurotoxic, as it is water-soluble and does not cross BBB. In contrast, unconjugated bilirubin is fat-soluble and readily crosses the BBB, to cause neurological damage.
- *Albumin binding of unconjugated bilirubin:* In plasma, unconjugated bilirubin is circulated in free form as well as albumin-bind form. Only free-form is neurotoxic.
- *Integrity of BBB,* which may be damaged by hypoxia, acidosis and sepsis to permit bilirubin crossing at lower serum levels and development of kernicterus.

Fig. 12.17: **Kernicterus.**

Pathology: Entry of free unconjugated bilirubin into brain leads to selective and irreversible destruction of neuronal cells. *Basal ganglia is the primary site of bilirubin staining/toxicity*, apart from dentate nucleus, auditory nucleus and hippocampus.

Clinically, kernicterus presents with following features in a deeply icteric baby:

- ***Early kernicterus*** (stage I) during first 24–48 hours, with poor sucking, lethargy and high-pitched shrill cry. These features indicate impending bilirubin encephalopathy and need for exchange transfusion, irrespective of bilirubin levels.
- ***Established kernicterus*** (stage II) with generalized hypotonia/rigidity, depressed Moro's and other neonatal reflexes, *sun-set sign* (visible upper sclera due to persistent downward gaze), opisthotonus and seizures **(Fig. 12.17)**.
- ***Terminal kernicterus*** (stage III) with generalized hypotonia, absence of cry and stupor in deeply icteric baby.

Mortality and risk of long-term neurological damage is very high in stage II/III disease, despite exchange transfusion, as irreversible neurological damage has already occurred.

Late complications of kernicterus include—(a) *cerebral palsy*, usually of choreo-athetoid or extra-pyramidal type, (b) sensory-neural *deafness*, and (c) *mental retardation* or learning disabilities. Brownish discoloration of teeth is common in severe neonatal hyperbilirubinemia.

Management: Prevention is the key of management in kernicterus with early phototherapy and exchange transfusion in indirect hyperbilirubinemia and prompt treatment of BBB impairing factors. However, once the neurological damage has developed, it is irreversible and management aims to improve quality of life.

12.14.5 NEONATAL CHOLESTASIS

Neonatal cholestasis, i.e. persistent elevation of conjugated bilirubin > 1 mg/dl or (> 20% of total serum bilirubin if it exceeds > 5 mg/dl) beyond 14th day of life, denotes inadequate excretion of conjugated bilirubin from hepatocytes into duodenum.

Etiology: Depending on the site of obstruction, neonatal cholestasis may be divided into: (a) neonatal hepatitis, (b) intrahepatic biliary atresia (IHBA), and (c) extrahepatic biliary atresia (EHBA)

While ~30–40% cases are idiopathic, two most common basic pathogenic mechanisms for neonatal cholestasis are *virus-induced liver cell injury* and *metabolic liver disease* **(Table 12.41)**.

It appears that neonatal hepatitis and EHBA are different manifestations of same pathological process, the difference being the timing of insult. Hepatic injury in early fetal life probably leads to EHBA, while late disease presents as neonatal hepatitis.

Clinically, these cases present with:

- Progressive obstructive jaundice from 2nd week of life.
- Typical *clay-colour* stools, which may be intermittently coloured due to incomplete obstruction in neonatal hepatitis *or* shedding of bilirubin-laden gut mucosa in stools.
- Hepatosplenomegaly with or without signs of hepatocellular dysfunction.
- Signs of primary etiology, e.g. intrauterine infections, metabolic disorders, etc.

Diagnosis rests on persistent conjugated hyperbilirubinemia with elevated S. alkaline phosphatase levels, though etiological evaluation needs USG to detect biliary tree anomalies, liver (HIDA) scan to detect excretory functions, liver biopsy and cause-specific investigations. While d/d between neonatal hepatitis and EHBA is not always easy, **Table 12.42** compares important distinguishing features of two entities.

Management of neonatal cholestasis includes: (a) general supportive measures, and (b) specific surgical interventions, e.g. modified *Kasai's procedure* for EHBA.

General Supportive therapy includes:

- *High caloric (125% of normal) low-fat, high-protein diet* with medium chain triglycerides, (e.g. coconut oil), which do not require bile acid for their absorption.
- *Fat-soluble vitamin* supplements with vitamin A (5000–25000 IU/day), vitamin D (2500–4000 IU/day), vitamin E (PO 50–400 IU/day) and vitamin K (IM 2.5 mg biweekly), along with other micronutrients in usual doses.
- *Anti-cholestatic agents*, e.g. cholestyramine (0.25–0.5 gm/kg/d q8hr) or ursodeoxycholic acid or UDCA (10–20 mg/kg/d q8hr) with/without phenobarbitone (3–5 mg/kg/d), to enhance bilirubin excretion, reduce cholesterol levels and reduce pruritis. Rifampicin 10 mg/kg/day may also be used to also reduce itching.
- *Treatment of complications*, e.g. ascites (salt/fluid restriction, diuretics) and hepatic failure.
- *Liver transplant* is the only definite treatment in severe cases, with success rate of >75% at good centers.

Some common cholestatic disorders in newborns are as follows:

Neonatal hepatitis denotes a heterogeneous group of conditions, all characterized by common histopathological features on liver biopsy, i.e. *distorted lobular architecture with massive giant cell transformation and canalicular cholestasis.*

Etiology: Nearly 40% cases are idiopathic, while remaining may be due to intrauterine infections or more rarely, metabolic disorders **(Table 12.47)**.

Clinically most of these babies are IUGR and present with slowly progressive jaundice beyond first week of life (as late as 3 months). Stools are *intermittently clay coloured*, signifying incomplete biliary obstruction.

TABLE 12.41: Neonatal cholestasis disorders

- **Intrahepatic cholestasis**
  - ***Neonatal hepatitis***
    - Idiopathic neonatal hepatitis (~50%)
    - Intrauterine (TORCH) Infections (45%)
    - Metabolic disorders (5–8%):
      - Cystic fibrosis
      - *Others:* Galactosemia, α_1-antitrypsin deficiency
    - *Others:* Hypothyroidism, total parenteral nutrition
  - ***Intra-hepatic biliary atresia (IHBA)***
    - Watson-Alagille syndrome
    - Caroli disease *(cystic dilatation of IHB ducts)*
    - Progressive familial intrahepatic cholestasis
- **Extrahepatic cholestasis**
  - Extra-hepatic biliary atresia (EHBA) (25–40%)
  - Choledochal cyst
  - Inspissated bile syndrome
  - Hypertrophic pyloric stenosis

TABLE 12.42: D/D Neonatal hepatitis *vs* EHBA

	Neo. Hepatitis	***EHBA***
Appearance	IUGR	Normal
Onset of icterus	Early	Late (>2 weeks)
Severity of icterus	Fluctuating	Progressive
Clay-Stools	Intermittent	Continuous
HSmegaly	Early	Late
U. urobilinogen	+/–	–
Alk phosphatase	↑	↑↑↑
SGOT/PT	↑↑	N/↑
α-fetoproteins	↑/N	N
IMIDA scan	Excretion	No excretion
Liver biopsy	Giant cells	Canal. hypoplasia
*Op.Cholangiogram**	Excretion	No excretion

Hepatosplenomegaly is invariably present, as also other features of intrauterine infections or metabolic disease.

Hepatic damage is usually progressive with ultimate development of *micronodular cirrhosis*, though some cases of idiopathic etiology may recover spontaneously.

Diagnosis rests on—(a) conjugated bilirubinemia, (b) liver biopsy, and (c) etiological investigations, e.g. serology for intrauterine infections, screening for metabolic errors, etc.

Management is largely supportive, as discussed earlier, unless the specific cause is identified and treatable. *Corticosteroids are of no benefit and not recommended*.

Extra-hepatic biliary atresia (EHBA) is the commonest anatomical cause of neonatal cholestasis, ~10 times more common than IHBA.

Clinical features: *Unlike neonatal hepatitis*, in EHBA: (a) most babies are apparently healthy with good birth weight, (b) stools are consistently clay-colored or 'cheesy-white' (except intermittent color due to shedding of bilirubin-laden gut mucosa), and (c) associated malformations, e.g. intestinal atresia, dextrocardia or polysplenia may be present. Untreated cases progress rapidly to develop biliary cirrhosis, as early as by 8th week of life.

Diagnosis rests on: (a) consistent rise in direct bilirubin and serum alkaline phosphatase levels, (b) USG for anatomical biliary tree status, (b) liver (HIDA) scan to demonstrate poor hepatic excretion, and (c) *confirmatory per-operative cholangiography.*

On biopsy, presence of ductal/ductular proliferation, ductular bile plug and fibrosis are more suggestive of EHBA than neonatal hepatitis.

Management: *Modified Kasai's procedure* (hepato-portoenterostomy) is the surgery of choice in EHBA, to use minute bile duct remnants in fibrous tissue of porta hepatis for bile drainage, which may be in direct continuation of intrahepatic ductules.

Success of the surgery depends on its timing, extent of bile-duct remnants and pre-existing liver damage. These cases must be operated as soon as possible to prevent irreversible hepatic damage. Kasai's procedure is successful in >80% cases if performed before 8th week, though long-term outcome is poor due to secondary complications, e.g. cholangitis.

Intra-hepatic biliary atresia (IHBA) is less common than neonatal hepatitis and EHBA. Among various types of IHBA, the commonest is ***Watson-Alagille syndrome,*** characterized by:

a. *Typical facial dysmorphism* with prominent forehead, hypertelorism, anti-mongoloid slant of eyes and flat nasal bridge,
b. *IHBA* with direct hyperbilirubinemia that usually presents later than EHBA/neonatal hepatitis (3rd–4th week), and
c. *Co-anomalies*, e.g. pulmonary stenosis, vertebral arch defects and tubulointerstitial nephropathy.

Treatment is largely supportive and long-term survival is relatively better than in EHBA, though pruritis, xanthomas and malabsorption is common.

Inspissated bile syndrome is usually a consequence of Rh-HDN, due to clogging of bile canaliculi by thick viscid bile, containing large amount of bile pigment.

Clinically, these cases present with persistent conjugated hyperbilirubinemia following severe hemolysis in neonatal period, which gradually recovers in next few months without any treatment.

12.15 PERINATAL INFECTIONS

Infections are major cause of perinatal morbidity, responsible for >40% neonatal deaths in India. Newborns are highly susceptible for infections due to immature defense mechanisms **(Table 12.43)** as well as exposure to variable bacterial flora during delivery or postnatal stay in the hospital. Various diagnostic/therapeutic interventions in intensive care units are further source of nosocomial infections in sick babies. Interestingly, male newborn is more prone for infections, perhaps due to possible locus of gene for immunoglobulin synthesis on X chromosome (?).

12.15.1 SUPERFICIAL NEONATAL INFECTIONS

Superficial skin infections, discussed in this section, are not only more common, but also serves as a portal of microbial entry for serious deep-seated infections or septicaemia

Umbilical sepsis *(omphalitis)* is one of the commonest superficial infection and potential source of septicaemia in newborns.

Etiologically, umbilical sepsis is usually due to *Staph. aureus* or *E.coli*, depending on local nursery profile and antiseptic practices.

Clinically, it presents with—(a) purulent, foul-smelling discharge, (b) peri-umbilical redness and induration, and (c) delayed separation of stump >7–10th day **(Fig. 12.18)**.

TABLE 12.43: Immature host-defenses in newborn

- Immature skin/mucus membrane barriers
- Immature physiological clearance, e.g. cough
- Immature immune mechanisms
  - Poor phagocytosis for innate immunity
  - Low IgM and secretory IgA levels*
  - Low IgG in preterms**
  - Low complement/opsonin activity
  - ↓ NK-cell activity
  - Lack of specific acquired immunity
- Antibiotic/drug therapy altering normal flora

*Only IgG is transferred transplacentally,
**as IgG transfer is maximum in last trimester.

Fig. 12.18: **Umbilical sepsis.**

Complications: Untreated umbilical sepsis may lead to three important complications: (a) local abdominal cellulitis, (b) neonatal septicemia, and (c) portal vein thrombosis, with extrahepatic portal hypertension in later life.

Diagnosis is clinical though umbilical swab should be sent for microbial diagnosis. However, a positive culture from umbilical site without clinical signs of sepsis indicates colonization and needs no treatment. However all cases need sepsis screening (*see* **Table 12.45**) to exclude neonatal septicaemia.

Treatment: Mild, uncomplicated umbilical sepsis only requires periodic cleaning of the discharge with a sterile wet/alcohol gauze, followed by topical application of an antibiotic (neomycin or bacitracin) or 0.5% gention violet 6-hrly.

Systemic antibiotics are indicated only in cases with severe umbilical sepsis or suspected neonatal septicemia. Umbilical catheterization should never be attempted in cases with umbilical sepsis.

Prevention of umbilical sepsis includes: (a) general maternal/neonatal hygiene, to reduce pathogenic colonization, (b) hand washing by nursery personnel before handling the baby.

Conjunctivitis *(ophthalmia neonatorum)*: Slight sticky eye discharge is common during first few days of life, which clears spontaneously and needs no treatment except intermittent cleaning with sterile wet cotton. However, presence of persistent/purulent discharge indicates neonatal conjunctivitis.

Etiologically, neonatal conjunctivitis is caused by organisms from: (a) maternal birth canal, e.g. *N. gonorrhoeae* or *C. trachomatis*, *or* from (b) hospital environment, e.g. *pseudomonas* or *staphylococci*, i.e. nosocomial conjunctivitis.

Clinically, gonococcal conjunctivitis presents within first 48 hours, chlamydial conjunctivitis after 5th day (usually unilateral) and nosocomial conjunctivitis at any age (usually purulent). Severity may vary from superficial conjunctivitis to secondary complications, e.g. keratitis, iridocyclitis and panophthalmitis.

Diagnosis is clinical, though gram staining and culture of discharge as well as microscopic examination of scrapping from tarsal conjunctiva (inclusion bodies in chlamydial disease) is essential for rational therapy.

Treatment: Regular eye wash with warm saline and topical antibiotics (Erythromycin 0.5% or Chloramphenicol 1.0%) are enough for mild conjunctivitis, while severe cases need organism-specific systemic antibiotics. A single dose of IV/IM ceftriaxone 25–50 mg/kg at birth is enough for gonococcal conjunctivitis while chlamydial infection must be treated with oral Azithromycin 20 mg/kg OD for 3 days, along with local eye irrigation. Topical antibiotic drops, e.g. Tobramycin is required in cases of other bacterial conjunctivitis.

Crede's method to instill 1% silver nitrate in eyes at birth to all newborns to prevent gonococcal conjunctivitis is no longer practiced due to low incidence and risk of chemical conjunctivitis.

Pyoderma are usually *staphylococcal* in origin and commonly seen over scalp, neck, groin, back and axilla in newborn. Occasionally, the focal lesion may spread *locally* to form abscess, cellulitis or pemphigus neonatorum (extensive bullous lesions with exfoliation) or *hematogenously* to cause neonatal septicemia or deeper infections, e.g. osteomyelitis.

Uncomplicated pyoderma may be punctured for gram staining/culture of pus, followed by topical antibiotics, e.g. *mupirocin*, 2–3 times a day. Systemic antibiotics are indicated only in extensive superficial lesions with cellulitis/abscess *or* suspected septicemia.

Oral thrush, due to transient and self-limiting *C. albicans* infection is very common even in normal newborns. Infection is usually acquired during passage from infected birth canal or from a nosocomial source.

Clinically, *oral thrush* presents as a white, adherent plaque with erythematous base on oral mucosa, tongue and palate that leaves punctate areas of bleeding on removal. *Invasive candidiasis* may develop in extreme preterms, critically sick newborns or after prolonged antibiotics.

Diagnosis is clinical, to be differentiated from *milk patch*—easy removable without leaving bleeding points.

Treatment includes topical application of antifungal agents, e.g. miconazole, clotrimazole, nystatin (2 lac U/5 ml glycerine) or 0.5% gention violet. Systemic antifungal therapy is not required for superficial candidiasis.

Napkin rash is a common problem associated with use of synthetic diapers, due to contact dermatitis, chemical irritation by urine/stools, and occasionally, secondary infection, e.g. candidiasis.

Clinically, it presents with well-demarcated confluent erythema over diaper region. Presence of red satellite pustules indicates candidal infections.

Management: Napkin rash is easily preventable by use of cotton diapers and frequent change of diapers to avoid excessive wetness and skin maceration. Uncomplicated cases respond well to topical application of coconut oil or a bland ointment, e.g. zinc calamine, while those with suspected candidal infection need topical antifungals, e.g. clotrimazole/miconazole. Mild steroid cream, e.g. clobetasone, may be used on acute irritating lesions.

Noma neonatorum (cancrum oris) is a rare but serious anaerobic infection in newborns (and in severely malnourished infants), characterized by acute, *rapidly progressive gangrene of buccal mucosa* that rapidly turns into perforating cheek ulcer. Secondary infection with pseudomonas is common.

Diagnosis is clinical and therapy includes intensive antibiotic therapy, though reconstructive plastic surgery is required in survivors.

12.15.2 NEONATAL SEPTICEMIA

Neonatal septicemia is a clinical diagnosis with *features of sepsis with or without positive blood/CSF cultures during first month of life*.

According to the time of onset, it may be divided in *early onset sepsis* (EOS) manifesting <72 hours of delivery *or late-onset sepsis* (LOS), with different predisposing factors and microbial etiology.

Risk factors: Neonatal sepsis is the commonest cause of neonatal mortality in India, with an estimated incidence of ~2–10%, depending on risk factors **(Table 12.44)**. Premature rupture of membranes, foul-smelling liquor amnii and complicated delivery with neonatal resuscitation are most important risk factors for EOS, while LOS is predominantly associated with prematurity/low birth weight, umbilical sepsis and nosocomial infections.

Table 12.44: Risk factors for neonatal septicemia

Early-onset sepsis
- ***Maternal factors***
  - Maternal fever <14 days before delivery
  - Foul smelling/meconium stained L. amnii
  - Prolonged rupture of membranes >24 hours
- ***Obstetrical factors***
  - Prolonged, difficult or instrumental delivery
  - Repeated unclean vaginal examinations

Late-onset sepsis
- ***Neonatal factors***
  - Preterm or small-for-date delivery
  - Superficial infections, e.g. umblical sepsis
  - Postnatal (milk) aspiration
- ***Nosocomial factors***
  - Neonatal resuscitation procedures
  - Invasic Intensive care procedures
  - Prolonged antibiotic therapy

Microbial etiology depends on the source and timing of infection.

EOS is usually caused by maternal flora of the genital tract, e.g. *E. coli, Klebsiella, Enterobacter, Listeria,* etc. Group B streptococci—the commonest cause of EOS in developed countries, is relatively uncommon in India.

LOS is usually a nosocomial infection due to organisms prevalent in hospital environment, e.g. *Staph. aureus, Klebsiella, Pseudomonas, Acinetobacter, enterococci, coagulase negative staphylococci* (CONS), etc. Fungal infections (*C. albicans*/non-albicans) are emerging as important cause of nosocomial LOS in NICUs.

Microbial profile of neonatal septicemia also depends on locally prevalent flora and infection-control practices. In general, *Klebsiella (~30%), S. aureus (~15%) and pseudomonas (~15%) are common pathogens in India*, with rising incidence of acenobactor, enterococci and CONS.

Clinical presentation of neonatal sepsis extends from silent bacteremia to multi-organ dysfunction, though most cases present with:
- ***Early clinical indicators***, e.g. refusal to feed, sluggish activity or irritability, excessive or high-pitched cry, respiratory distress or apneic spells, seizures, diarrhoea and/or vomiting.
- ***Signs of systemic stress,*** e.g. hypothermia, sclerema, pallor, cold-clammy skin, circumoral cyanosis, exaggerated icterus and purpuric spots. Peripheral perfusion may be poor with capillary filling time exceeding 3 seconds.
- ***Signs of localized infection***, e.g. umbilical sepsis or pyoderma, pneumonia, meningitis (~20–30%), necrotizing enterocolitis and bleeding diathesis, e.g. DIC. Pneumonia and meningitis is more common in EOS and LOS respectively.

Diagnosis of neonatal septicemia usually rests on clinical suspicion and presence of high-risk *factors.*

However, laboratory confirmation requires:
- ***Indirect evidences,*** e.g. peripheral smear, are useful screening tests for early diagnosis of neonatal septicemia. A combination of indirect evidences is often termed *sepsis screen* **(Table 12.45)**, with specificity

Table 12.45: Sepsis screen in newborns

- **Hematological findings (criteria)**
  - Leukopenia (<5000 cells/mm^3)
  - Absolute neutropenia (<1800 cells/mm^3)
  - Immature (Band) cell count >20% (I:T Ratio > 2)
  - Thrombocytopenia <1,00,000 cells/mm^3
- **Positive acute phase reactants**
  - C-reactive protein (CRP) >8 mg/L
  - Micro ESR > 15 mm/FHR

I:T ratio: Immature to total neutrophil count ratio.

and sensitivity of >90%, if at least two parameters are fulfilled. Two negative sepsis screens 24 hours apart, practically exclude neonatal sepsis. CRP alone has a sensitivity and specificity of 87% and 83% respectively.

- ***Direct evidences,*** i.e. positive culture from blood, CSF, pus, etc. is the gold standard for diagnosis of neonatal sepsis. However, a sterile culture does not exclude the diagnosis, specially if empirical antimicrobial therapy was started before sample collection. BACTEC radiometry, though costly, is very useful for earlier microbial identification than conventional culture.
- ***Antigen-detection tests*** (Latex-agglutination test, ELISA) or polymerase chain reaction (PCR) are specially useful to identify causative pathogens in culture-sterile cases.
- ***Evidence of focal infections,*** e.g. abnormal CSF findings, urine-analysis, pus cells in umbilical discharge, gastric wash, etc. *CSF examination is indicated in all cases of severe sepsis,* though reports should be interpreted carefully, as newborns, specially preterms, have higher protein and cell content in CSF, than in older children.

Management of neonatal septicemia may be divided into antimicrobial therapy and supportive management.

- ***Antimicrobial therapy*** should be started empirically after collection of cultures and modified after culture/sensitivity reports. Choice for empirical therapy may vary in different centers, based on local flora and sensitivity patterns **(Table 12.46)**. In all cases, antibiotics should be given via IV route and continued for minimum 10 days in cases without meningitis and for minimum 21 days in presence of meningitis.
- ***Supportive therapy*** depends on individual needs and includes:
  - Maintenance of temperature with warmer care,
  - Oxygen/ventilatory support
  - Circulatory support with IV fluids, volume expanders (blood/plasma) and vasopressors.
  - Fluid and electrolyte correction
  - Adequate oral or parenteral nutrition
  - Treatment of complications, e.g.
    - Hypoglycemia (IV dextrose 10% 2 ml/kg stat)
    - Apneic spells (stimulation, aminophylline)
    - Hyperbilirubinemia (phototherapy/exchange)
    - Bleeding tendency (vitamin K, FFP, platelets)
    - Seizures (anticonvulsants)
  - Surgical interventions, e.g. drainage of pus, etc.

Role of immunoglobulins and exchange transfusion in neonatal septicemia is controversial but may be useful in some critically sick cases.

Prevention of neonatal septicemia involves: (a) early detection and management of high-risk factors, (b) six *"cleans"* at the time of delivery (*clean hands, clean delivery surface, clean perineum, clean blade to cut the cord, clean/dry cord and clean towels),* and (c) prevention of nosocomial infections.

Role of prophylactic antibiotics is controversial though may be indicated in presence of high-risk factors for neonatal septicemia. However, intrapartum antibiotic prophylaxis with a single dose Penicillin or cefazolin, 4 hours before delivery is indicated to prevent GBS sepsis in cases of PROM, maternal fever and antenatal GBS colonization in rectovaginal swabs.

Listeriosis (L. monocytogenes) is an emerging cause of meningitis/septicemia in newborns (or immunodeficient children). It is primarily an epizootic infection, transmitted to humans via consumption of infected animal products, e.g. milk or faeces-contaminated vegetables. *Maternal listeriosis* is asymptomatic, but with higher risk of abortion, stillbirth or premature delivery.

Neonatal listeriosis is acquired during delivery via infected birth-canal or as nosocomial infection and typically presents as meningitis with septicemia. *diagnosis* rests on blood and CSF cultures, along with simultaneous cultures from maternal genital tract. *Treatment* of choice is Ampicillin alone or with an aminoglycoside, followed by vancomycin in non-responders. Listeria is not susceptible to third-generation cephalosporins.

TABLE 12.46: Antimicrobial therapy in neonatal septicemia

Empirical therapy	
NS without meningitis (minimum 7–10 days)	
First-line	: Ampicillin + Aminoglycoside
Second-line	: Piperacillin tazobactam + Aminoglycoside
NS with meningitis (minimum 21 days)	
First-line	: Cefotaxime + Aminoglycoside **or** Vancomycin + Aminoglycoside
Second line	: Meeropenem + Aminoglycoside **or**
Specific therapy	
E. coli/Klebsiella	: Cefotaxime + Aminoglycoside
Pseudomonas	: Ceftazidime + Aminoglycoside
Staph. aureus	: Cloxacillin/vancomycin
Listeria	: Ampicillin

Daily IV doses in newborn (in 2–3 divided doses):
Ampicillin/Cloxacillin/Piperacillin all (100–150 mg/kg/d),
Cefotaxime/Ceftazidime/Ceftriaxone all (100–150 mg/kg)
Gentamycin (5–8 mg/kg), Amikacin (15 mg/kg),
Meropenem (120 mg/kg), Vancomycin (30 mg/kg)

12.15.3 NEONATAL NECROTIZING ENTEROCOLITIS

Neonatal necrotising enterocolitis (NEC) is a serious GIT complication in *preterm and critically sick or septic newborns*, characterized by *progressive abdominal distension, hematochezia and vomiting or retention of nasogastric feeds.*

Incidence: NEC may develop in ~3–5% of NICU cases, most common in: (a) extreme preterms (<32 weeks), and (b) critically sick newborns, e.g. birth asphyxia, sepsis, shock and acidosis. Early enteral feeding in these cases is an additional risk factor.

Pathogenesis is still evolving, but two factors are most important and inter-related:

a. *Ischemic gut mucosal injury* due to shock or hypoxia, leading to stasis and infection, and
b. *Local enteral Infection* due to early feeding or septicemia, aggravating the mucosal injury.

Irrespective of primary event, the net result is intestinal stasis and infection, further complicated by necrotizing mucosal injury, perforation and peritonitis.

Clinically, NEC usually presents on 3–4th day, with a triad of:

- Gross, tender, tympanic abdominal distension suggestive of paralytic ileus.
- Retention of nasogastric feeds (>25% of previous feed) or vomiting,
- Hematochezia, i.e. per-rectal bleeding, with/without upper GIT bleeding

In addition, systemic signs of sepsis, shock or other perinatal complications are often present.

Diagnosis is largely clinical, supported by radiological findings **(Fig. 12.19)**. *Pneumatosis intestinalis*, i.e. presence of intramural gas bubbles in intestinal wall is pathognomic radiological feature of NEC, though frequently missed. *Other X-ray features* include fixed-loop pattern, bowel-wall edema, air in portal/hepatic vein *or* pneumoperitoneum, suggestive of intestinal perforation.

Supportive investigations include stool examination for hematochezia, blood/stool cultures and other relevant investigations, e.g. serum electrolytes.

Severity of NEC may be staged (***Bell's criteria***) as:

- ***Stage I (Suspected NEC)*** with mild distension, retention of feeds/vomiting, minimal X-ray abnormality.
- ***Stage II (Definite NEC)***, with marked distension, hematochezia, absent bowel sounds and/or pneumatosis intestinalis on X-ray.
- ***Stage III (Advanced NEC)*** with DIC, shock, peritonitis and radiological signs of pneumoperitoneum or extraintestinal (portal vein) gas.

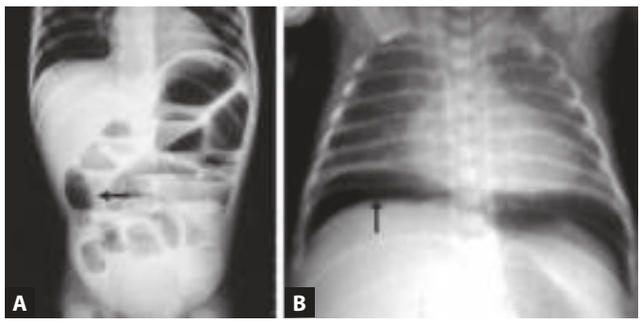


Fig. 12.19: Neonatal necrotizing enterocolitis: (A) Pneumatosis intestinalis; (B) Gas under diaphragm.

Management of these cases include:

- Management of primary causative factor, i.e. perinatal complications.
- Nil orally with continuous nasogastric drainage to rest the bowel and drain gastric secretion/bleeds.
- IV fluid therapy, to provide nutrition and maintain fluid and electrolyte balance.
- Systemic antibiotics to control infection. Local gut sterilization is not routinely indicated.
- Blood/packed cell transfusions, in cases with severe GIT bleeding.
- Constant monitoring of abdominal girth and other vital/laboratory parameters
- Surgical intervention in perforation or peritonitis.

Enteral feeding may be restarted gradually after 48–72 hours of the control of GIT bleeding, absence of abdominal distension and appearance of bowel sounds; though recurrences are not uncommon.

Outcome: With best possible treatment, mortality is nil in stage I, 5–10% in stage II and >50% in stage III disease.

12.15.4 INTRAUTERINE INFECTIONS

Term intrauterine (IU) infections denotes *in utero fetal infection, either transplacentally or as an ascending infection from maternal birth canal*.

IU infections are the commonest cause of fetal loss (abortions/stillbirths), congenital malformations and intrauterine growth retardation (IUGR) in India. While infection in first trimester usually results in fetal loss or congenital malformations, later infections cause IUGR.

Etiology: IU infections are usually viral, though may also be caused by many bacterial, protozoan and spirochetal agents **(Table 12.47)**. In clinical practice, common IU infections are popularly referred with an acronym TORCH—***T***oxoplasma Gondi, ***O***thers, ***R***ubella, ***C***ytomegalovirus disease (CMV) and ***H***erpes simplex infections.

Clinical presentation: Live born babies with IU infections usually present with following features at birth **(Table 12.48)**, though some manifestations may develop or diagnosed at a later age.

- ***History of maternal illnesses***, e.g. fever, rashes, lymphadenopathy, jaundice and vaginal lesions

TABLE 12.47: Common intrauterine infections

a.	**Viral**	Rubella, CMV, HSV, HBV, HIV Varicella, mumps, parvovirus B19
b.	**Bacterial**	Tuberculosis, gonococci gram-ve organisms, listeriosis
c.	**Spirochetal**	Syphilis
d.	**Protozoal**	Toxoplasmosis, malaria
e.	**Others**	Mycoplasma, chlamydia

TABLE 12.48: Clinical indicators of intrauterine infections

- History of maternal infection
- Intrauterine growth retardation (IUGR/LBW)
- Hepatosplenomegaly and/or Jaundice
- Purpura
- *CNS:* Microcephaly, hydrocephalus, mental retardation
- *Ocular:* Microphthalmia, cataract, chorioretinitis
- Hearing impairment
- Congenital malformations, e.g. CHDs
- *Others:* Skin rash/vesicles, pneumonia, etc.

during pregnancy is present in >50% cases, though missed frequently.

- ***Low birth weight*** *(IUGR)* is the commonest manifestation in 60–70% babies. However, babies with congenital syphilis tend to be large-sized due to hydrops fetalis.
- ***Hepatosplenomegaly*** is present in 50–60% cases, with/without evidence of active liver disease. Neonatal *jaundice* is common in Toxoplasmosis and CMV infection.
- ***Purpuric lesions*** due to thrombocytopenia are common in CMV and congenital rubella, though serious internal bleeds are rare.
- ***Meningoencephalitis,*** is usually sub-acute and presents with microcephaly (rubella or CMV), hydrocephalus (toxoplasmosis) intracranial calcifications (CMV, rubella), mental retardation and seizure disorders. Intracranial calcifications are typically periventricular in CMV and diffusely nodular in toxoplasmosis.
- ***Ocular abnormalities:*** Extrinsic abnormalities, e.g. micropthalmia, microcornea, corneal opacities and cataracts are more common in congenital rubella. Presence of uveitis or interstitial keratitis indicates CMV and congenital syphilis respectively. Chorioretinitis is present in many infections and typically *central in toxoplasmosis, peripheral with normal macula in CMV* and *salt-pepper type in rubella* infections. Chronic retinopathy may leads to optic atrophy, strabisumus and searching nystagmus in older children.
- ***Hearing impairment*** is common in congenital rubella and CMV infections.
- ***Congenital heart diseases*** are common in congenital rubella, specially PDA or sub-valvular PS.
- ***Other manifestations*** include skin vesicles in herpes simplex, rash or snuffles in congenital syphilis, pneumonia and neonatal septicemia.

Diagnosis of IU infections depends on:

- *Presence of clinical indicators* **(Table 12.48)** or antenatal history suggestive of maternal infection.
- *Non-specific cord IgM levels* of >20 mg/dl indicate possibility of IU infection and may be used as a screening test. However, it has no differentiating value between various causes.
- *Specific serology* ***(TORCH screen)*** for organism specific IgG and IgM antibodies. Single IgG titers are unreliable due to passive transplacental transfer from mother. IgM titers are more reliable and indicate actual fetal infection.
- Serodiagnosis of any IU infection requires positive IgM titers *or* IgG titers multi-fold higher than maternal values *or* rising IgG values after 3–4 weeks.
- *Isolation of specific etiological agent* by microbiology or PCR testing is confirmatory, though rarely possible.
- *Relevant investigations:* X-ray skull and long bones, e.g. knee are indicated in all cases to detect, e.g. intracranial infections (CMV, toxoplasmosis), osteochondritis, periosteal reaction, and metaphysitis in long bones (congenital syphilis), longitudinal linear radiolucent areas with increased bone density (congenital rubella).

D/D of common IU infections is given in **Table 12.49**, while some are discussed in detail, as follows.

Congenital rubella syndrome (CRS) is consequence of rubella infection in previous non-immune pregnant mothers, which produces mild viral illness in pregnant mothers, but with devastating effect on fetus. For acquired infection, *see Ch 10.18.*

Mode of infection: Fetal infection is acquired transplacentally and risk of transmission is highest (~90%) when mother is infected in first trimester. Infection beyond 20th week is rarely associated with CRS, except sensory-neural deafness.

Clinical features of CRS include—(a) IUGR, (b) neurological signs, e.g. microcephaly and mental retardation, (c) ocular signs, e.g. congenital cataract, microphthalmia, microcornea, salt-pepper retinopathy, etc., (d) sensorineural hearing loss, (e) hepatosplenomegaly with/without jaundice, (f) anemia and thrombocytopenic purpura and (g) congenital heart diseases, specially *PDA or subvalvular PS* **(Fig. 12.20)**.

Diagnosis usually rests on specific serology, i.e. (a) elevated IgM titers in cord/neonatal blood, or (b) >4-fold higher IgG titers in newborn than in mother, or (c) rising IgG titers after one month. Viral isolation from nasopharynx or urine is confirmatory, but rarely feasible.

Management: Prevention of CRS revolves around prevention of maternal infection during pregnancy by (a) MMR immunization in childhood or unimmunized women in reproductive age, (conception should be avoided at least 3 months after immunization), or (b) avoidance of contact with suspected case during pregnancy, including a case of CRS (as virus may be shed up to 1 year).

TABLE 12.49: Comparative features of important intrauterine (TORCH) infections

	Rubella	*CMV*	*Toxoplasmosis*	*HSV*	*Syphilis*
Mode of transmission	TP	TP + PP + BM	TP + PP	PP + TP	TP + PP
Risk of transmission					
Pre-pregnancy infection	–	–	–	–	Uncommon
First trimester infection	90%	40%*	20% (severe)	Rare	100%
Late trimester infection	10%	40%*	60% (mild)	Rare	100%
Infection during delivery	–	40%	—	5–50%*	100%
Clinical features					
IUGR	+++	+++	+	Nil	Nil
Hepatosplenomegaly	+++	++	++	++	++
Bleeding	+++	+++	++	Rare	Rare
Neurological					
Microcephaly	++	+++	Hydrocephalus	+	+/–
Calcifications	–	Periventricular	Diffuse	–	–
Mental retardation	++	++	+	+/–	–
Meningoencephalitis	–	–	–	++	+
Ocular					
Microphthalmia	+	+	–	+	–
Cornea/Uveal tract	Opacity	Uveitis	Uveitis	Keratitis	Int. keratitis
Cataracts	+++	+	+	+	+/–
Chorioretinitis	Salt-pepper	Peripheral	Central	+	–
Deafness	++	++	+/–	–	+
Skin lesions	–	–	–	++	++
Systemic illnesses	CHD	Pneumonia	Pneumonia	Bony lesions	
Diagnosis	Serology	Serology	Serology	Clinical	VDRL, X-ray
Prevention	MMR	–	Maternal Rx	LSCS	Maternal Rx
Treatment**	None	Ganciclovir	Pyrm+sulpha	Acyclovir	Penicillin

TP: Transplacental infection, **PP:** Peripartum infection during vaginal delivery, **BM:** Infection via breast milk,
*in primary infection during pregnancy, < 1% in recurrent infection. ** *See* text for details

Fig. 12.20: Congenital Rubella Syndrome: (A) Microphthalmia with microcornia (*Inset:* Corneal opacity); (B) Celery-stalk appearance on X-ray knee.

Accidentally exposed and unimmunized pregnant mothers should be screened serologically, immediately and after 4 weeks of exposure. Risk of CRS is negligible in seropositive mothers at the time of exposure. However, those who seroconvert after exposure have maximum risk of CRS and should be counselled accordingly. If abortion is not an option, immunoglobulin prophylaxis is advisable immediately after exposure, to reduce risk of CRS.

Cytomegalovirus disease: Neonatal CMV infection is a consequence of primary maternal infection during pregnancy with risk of transmission being ~40%. Maternal reinfection or reactivation of previous infection is unlikely to produce neonatal disease. For acquired infection, *see Ch* 10.24.3.

Mode of infection: Neonatal CMV infection may occur: (a) *in utero* during maternal viremia after primary infection in pregnancy, (b) *during delivery*, by the virus present in genital passage, or (c) *post-natally* by infected breast milk or blood products. Maternal infection in

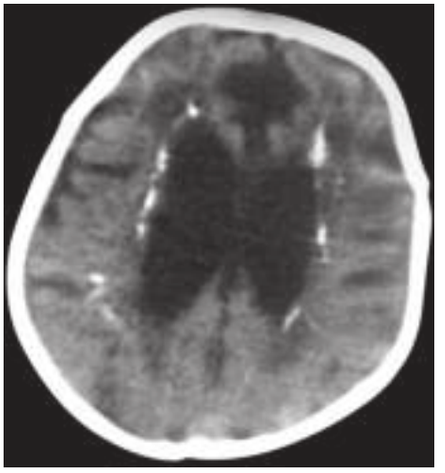


Fig. 12.21: **Periventricular calcification in congenital CMV infection.**

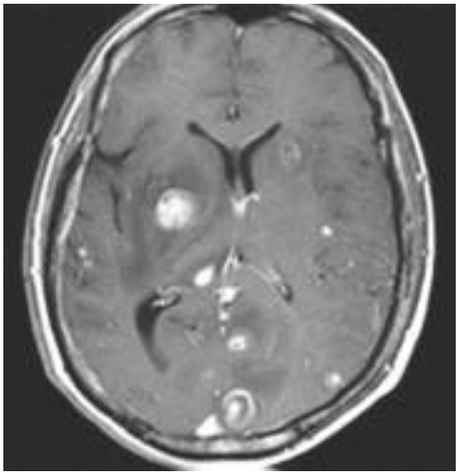


Fig. 12.22: **Diffuse intracranial calcifications and lesions in toxoplasmosis.**

early pregnancy is usually associated with more severe fetal disease.

Clinical manifestations depend on timing of infection and divided into three categories:

a. *Asymptomatic infection*, but with late developmental abnormalities (15%), e.g. deafness, mental retardation, spasticity and microcephaly.
b. *Symptomatic but not life-threatening infection*, with – (a) IUGR, (b) neurological signs, e.g. microcephaly, intracranial periventricular calcification **(Fig. 12.21)**, hearing deficit, mental retardation, etc., and (c) ocular signs, e.g. peripheral chorioretinitis without macular involvement.
c. *Acute sepsis-like manifestations* with—(i) hepato-splenomegaly, (ii) thrombocytopenic purpura, (iii) severe jaundice, and (iv) pneumonitis.

Diagnosis usually rests on serology though d*efinitive diagnosis* is possible by virus isolation or PCR testing in urine or saliva.

Treatment: *IV Ganciclovir* (6 mg/kg/dose q12hr) or PO Valganciclovir (16 mg/kg/dose q12hr) for 20 days is the drug of choice for acute manifestations, e.g. preumonitis or chorioretinitis, along with standard/hyperimmune *IVIG* (500 mg/kg/alternate day 10 doses). However, its utility in CNS disease is not established. *Foscarnet* is another alternative, under evaluation.

Congenital toxoplasmosis is a consequence of maternal infection during pregnancy, specially in last trimester. Fetal infection due to pre-pregnancy infection is extremely rare.

Mode of infection: Fetal infection is acquired trans-placentally, with risk of transmission being ~60% in last trimester infection, ~3–4 times higher than in first trimester infection.

Clinically, congenital toxoplasmosis may present with: (a) prematurity and IUGR, (b) neonatal disease with anemia, purpura, jaundice, and neurological disease, or (c) neuro-ocular sequelae of untreated infections in later life.

Characteristic features include—(a) *neurological disease* with hydrocephalus, diffuse intracranial calcifications **(Fig. 12.22)** and seizures; or (b) *ocular disease* with central choreoretinitis and secondary optic atrophy.

Diagnosis usually rests on elevated Toxo-IgM levels, though presence of tachyzoites in placenta on immuno-fluorescent staining) *or* positive CSF-PCR is confirmatory.

Treatment is of limited value in severely affected newborns, as the damage has already occurred. It should begin as early as possible and includes:

- ***Severe disease*** are treated with PO Pyrimethamine (1 mg/kg/day for 6 months than 0.5 mg/kg/day for next 6 months) and Sulfadiazine (100 mg/kg/day for 12 months, along with Folinic acid 10 mg alternate days. Steroids are indicated for 8–12 weeks in cases with acute inflammatory injury, e.g. chorioretinitis or elevated CSF protein > 1 gm.
- ***Mild or subclinical cases b***orn to a mother with definite primary infection may be treated less intensive regimens for shorter duration.

Prevention involves treatment of maternal infection during pregnancy with PO Spiromycin (2 gm/day) from 20th week onwards, along with Sulfadiazine (75 mg/kg/day) and Pyrimethamine (25 mg BD for 2 days, than OD for 7 days than biweekly). Folinic acid (5 mg bi-weekly) should be given with Pyrimethamine to prevent folic acid deficiency.

Congenital syphilis is a rarity in recent years due to early recognition and treatment of maternal disease.

Mode of infection: *Congenital syphilis* is usually acquired as transplacental infection during spirochetemia in mother, or rarely at the time of delivery through infected

TABLE 12.50: Late clinical stigmata of congenital syphilis

Bony changes (due to chronic periosteitis)
- Frontal bossing
- *Olympian brow* (prominent forehead)
- *Saddle nose* (depressed nasal bridge)
- *Perforated nasal septum* (due to snuffles)
- *Higouménaki's sign* (thick sternoclavicular joints)
- *Saber shins* (anterior bowing of Tibia)
- *Scaphoid scapula* (convex medial border)

Dental abnormalities (manifests ~6 years of age)
- *Hutchinson teeth* (barrel-shape upper incisors)
- *Notched teeth* with abnormal enamel and severe caries
- *Mulberry molars* (multi-cuspid lower first-molars)

Residual mucocutaneous lesions
- *Rhagades* (Spoke-like perioral/perianal scars)

Hypersensitivity manifestations
- Interstitial keratitis with/out corneal opacities
- *Clutton joints** (painless joint swellings)

*due to intermittent syonovitis, specially at knee

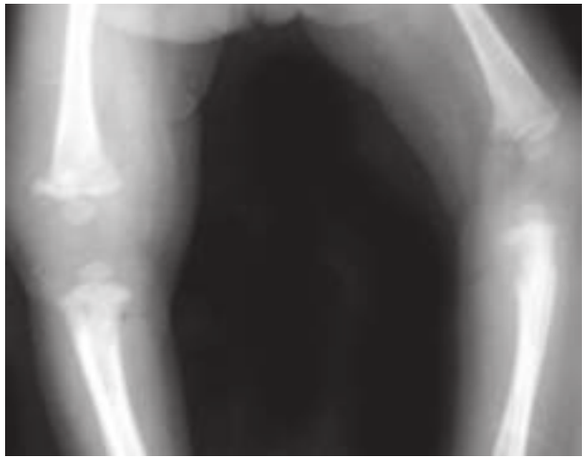


Fig. 12.23: Congenital syphilis : Periosteitis and osteochondritis at the ends of long bones.

birth canal. Infection is usually transmitted in last trimester, though spirochetes may cross placenta at any stage.

Risk of transmission is highest (~100%) in mothers with recent infection, decreases gradually and unlikely after 5 years of maternal infection.

Clinical manifestations: Early trimester infections often lead to abortions, stillbirths (40%) or hydrops fetalis due to severe anemia, while late trimester infections are often associated with *large placenta* and present as follows (IUGR is rare).

a. ***Early manifestations*** during first 2 years of life, are analogous to secondary syphilis, including Failure to thrive, generalized erythematous rash, Nasal snuffles, painful and restricted limb movements (pseudoparalysis), hepatosplenomegaly and pan/bicytopenia. Pneumonia and meningitis may be present.
b. ***Late manifestations (stigmata)*** after 5–10 years, due to chronic inflammatory changes in skin, bones and teeth, *or* hypersensitivity **(Table 12.50)**.

Diagnosis may be confirmed by dark field microscopy, FTS-ABS IgM or serial VDRL with rising titers after one week. A single VDRL titer >4 times of the mother or Positive VDRL in CSF may also be considered as diagnostic. VDRL may be false-positive in babies of infected mothers due to transplacental transfer of antibodies. *X-ray knee joint* may be diagnostic in a suspected case, showing periostitis and osteochondritis at the ends of long bones **(Fig. 12.23)**.

CSF examination is indicated in all cases for biochemistry and VDRL test, as longer penicillin therapy is required in cases with CNS involvement. However, CNS involvement is possible without CSF abnormalities.

Treatment of a baby born to VDRL positive mother depends on anticipated risk of infection. Adequate maternal therapy, if received at least 30 days prior to delivery, virtually eliminates the risk of transmission.

All other cases must be treated either with IV Crystalline Penicillin G (50,000 IU/kg/dose 8–12 hourly) *or* IM Procaine penicillin (50,000 IU/kg once a day) for 10–14 days. Longer therapy (3 weeks) is necessary in cases with CNS involvement.

Perinatal HSV infection is a consequence of primary or re-activation HSV infection in mother with active disease during pregnancy. For acquired infection, *see* Chapter 10.24.1.

Mode of infection: HSV infection is usually acquired during delivery through infected birth canal (peripartum). Rarely, baby may be infected *in utero* (<5%) or as postnatal nosocomial infection.

Clinically, peripartum infection presents with signs of active disease, e.g. typical skin/mucosal lesions (grouped vesicles), meningitis and respiratory distress during 1st week. However, early *in utero* infection may present with sequelae, e.g. microcephaly, microphthalmia, chorioretinitis and old skin scars (suggestive of *in utero* vesicles).

Diagnosis is largely clinical but may be confirmed by the viral culture or PCR from urine or saliva in first two weeks of illness. *Tzanck* cells are also present in vesicular scrapping.

Treatment: Acyclovir therapy (IV 20 mg/kg/dose TDS for 14–21 days) is the mainstay of treatment in perinatal HSV infection, apart from supportive and symptomatic care.

Prevention: Obstetrical care in mother with genital HSV includes—(a) elective LSCS to avoid vaginal passage, (b) Viral cultures from eyes, nose, mouth, urine and stools of baby at 48 hours, and (c) prophylactics acyclovir therapy to baby, if mother is symptomatic at the time of delivery.

Some other important intrauterine infections, e.g. congenital tuberculosis, congenital malaria and perinatal HIV infection have been discussed in respective chapters.

12.16 NEONATAL SEIZURES

Seizure is a common neonatal emergency, seen in ~0.5% of term and ~2.0% of preterm newborns. Apart from sudden death due to choking or aspiration, seizures may also lead to persistent hypoxic brain damage and long-term sequelae.

Clinical types: Neonatal seizures often present differently than in older children and adults with atypical manifestations, e.g.

- *Subtle seizures,* either with *minimal motor activity* involving eyes (vacant stare, upward gaze), face (chewing, tongue thrusting, lip smacking), or limbs (paddling, cycling, boxing); *or sudden autonomic disturbances*, e.g. apnea, tachycardia/bradycardia, etc.
- *Clonic seizures* with associated EEG abnormality, which carry best prognosis.
- *Tonic seizures* or decerebrate posture, usually without EEG changes.
- *Myoclonic seizures* with jerky movements of limbs or trunk, carry worst prognosis in terms of neurodevelopmental outcome.

Neonatal seizures may also be classified as: (a) Electroclinical seizures with clinical as well as EEG changes, (b) Clinical seizures without EEG changes, and (c) Electric seizures with abnormal EEG but no clinical presentation.

Etiology: Metabolic seizures are most common in previously healthy newborn, while sick babies may convulse due to many causes, as follows:

- *Hypoxia:* HIE or intracranial hemorrhage.
- *Infections:* Meningitis, intrauterine infections, etc.
- *Metabolic:*
  - Hypoglycemia
  - Hypocalcemia with/without hypomagnesemia
  - Pyridoxine dependency
  - Dyselectrolytemia
  - Inborn errors of metabolism (rare)
- *CNS malformations:* Microcephaly, hydrocephalus
- *Kernicterus*
- *Vascular:* Polycythemia, severe dehydration
- *Iatrogenic:* Narcotic withdrawal, aminophylline, accidental injection of local anaesthetics over fetal scalp during delivery—analgesia.

Diagnostic approach: Immediate control of seizures is more important than to identify its etiology. However, subsequent clinical evaluation and relevant investigations are necessary for etiological diagnosis and rational treatment, to prevent further attacks.

Diagnostic approach in these cases involves:

- ***Careful history*** regarding
  - Age of onset **(Table 12.51)**.
  - Antenatal maternal infections or medications, etc.
  - CNS anomalies or metabolic errors in family.
  - Birth asphyxia, risk factors of neonatal sepsis.
  - Delayed feeding (hypoglycemia), etc.
- ***Clinical examination*** *for signs of*:
  - Sepsis/meningitis, e.g. sick child, bulging AF, etc.
  - Neural tube defects, abnormal head size
  - Intrauterine infections, e.g. low birth weight, hepatosplenomegaly, etc.
  - *Apparently well child* (metabolic seizures).
- ***Laboratory investigations,*** including:

  Step I. Base-line investigations
  - Sepsis screen: Blood counts, CRP, etc.
  - Metabolic screen: B. Sugar, S. Ca^{++}, Mg^{++}
  - CSF examination including bacteriology
  - Cranial USG for malformations or bleeds

  Step II. Second-line investigations
  - *Neuroimaging:* CT/MRI, EEG
  - Serological (TORCH) screening

  Step III. Select cases with unexplained seizures
  - Screening tests for inborn errors of metabolism, e.g. arterial blood gas analysis, serum ammonia, lactate/pyruvate, etc.

TABLE 12.51: Causes of neonatal seizures with age of onset

Day 1 seizures
- Birth asphyxia/hypoxic ischemic encephalopathy (HIE)
- Pyridoxine dependency
- Local anaesthetic injection in fetal scalp

Day 2–3 seizures
- *All of the above,* ***plus***
- *Metabolic:* Hypoglycemia, hypocalcaemia, hypomagnesemia
- Birth injuries, e.g. Intracranial haemorrhage
- Developmental CNS malformations
- Tetanus neonatorum
- Narcotic withdrawal

Day 3–28 seizures
- *All of the above except narcotic withdrawal,* ***plus***
- Infections, i.e. septicemia, meningitis
- *Metabolic:* Late-onset hypocalcemia
  Pyridoxine dependency/deficiency
  Inborn errors of metabolism
- Benign familial neonatal seizures (5^{th} day fits)
- *Others:* Kernicterus

Differential diagnosis: Apart from etiological differentiation, neonatal seizures should also be differentiated from seizure mimics, e.g. jitteriness and being neonatal myoclonus.

Jitteriness is common in normal newborns during first 48 hours, characterized by fast, symmetrical and rhythmic movement of limbs without gaze abnormality, which can be easily stimulated by just touching the baby and can be rapidly abolished by mild restrain or passive flexion of limbs. Persistent and severe jitteriness may be a sign of: (a) cerebral hypoxia, (b) metabolic problems e.g. hypoglycemia, hypocalcemia, etc., (c) narcotic withdrawal, and (d) congenital thyrotoxicosis.

Benign myoclonus is sudden jerky movement of limbs in a newborn while asleep, which disappear on waking. Baby is otherwise normal and myoclonus subsides by 2–3 months without any treatment, with long term adverse outcome.

Management: All neonatal seizures need emergency hospitalization and the first priority lies in immediate control of seizures, irrespective of cause. Important steps in management include:

Step I. Ensure airway patency and adequate ventilation by cautious low-pressure suction, proper positioning (lateral/prone) to prevent aspiration and oxygen supplementation.

Step II. Establish an IV line for anticonvulsants, drugs and fluid-electrolyte correction. An IV anticonvulsant (as in step V) may be given at this stage, if seizures are life-threatening and unlikely to be metabolic.

Step III. Collect blood samples for *metabolic screen*, i.e. B. sugar, calcium and magnesium, as well as quick clinical evaluation.

Step IV. Empirical correction for common metabolic causes, specially in apparently healthy and term babies. This step involves step-wise correction of problems, as follows:

- IV Dextrose 10%, 2 ml/kg as bolus, followed by continuous infusion (6–8 mg/kg/min). If seizures are not controlled, then–
- IV Calcium gluconate 10%, 2 ml/kg (1:1 dilution in distilled water), slowly over 5–10 minutes with cardiac monitoring for bradycardia. If seizure are not controlled, then–
- IM Magnesium sulphate 50%, 0.2 ml/kg as bolus. If seizure are not yet controlled, then–

Step V. Specific anticonvulsant therapy should begin as early as possible, if metabolic cause is unlikely *or* no response to metabolic corrections (Step IV). Various anticonvulsants are used in step-wise manner with monitoring of response, as follows:

- IV Phenobarbitone 20 mg/kg, slowly over 20 minutes. Doses may repeated as 5–10 mg/kg twice after every 30 minutes (Total 40 mg/kg) in non-responders. Still, if seizures continue.
- IV Phenytoin 20 mg/kg, diluted in distilled water, slowly (<1 mg/kg/min) over 10–15 minutes IV **or** preferably IV Levetiracetam 50 mg/kg over 20 minutes. Fosphenytoin is preferred to Phenytoin in equivalent doses, if available. Still, if seizures continue.
- IV Midazolam (0.15 mg/kg as bolus followed by continuous infusion as 0.5–1 µg/kg for the ease of dosage titration. However, considering side-effects, e.g. sedation, benzodiazepines should not be used for long-term control. IV Lidocaine 2 mg/kg bolus followed by 6 mg/kg/hour may also be used to control refractory seizures, titrated down gradually

  IV Pyridoxine 50–100 mg slowly under EEG monitoring may be tried in some refractory cases with dramatic response in cases of pyridoxine deficiency/dependency seizures, which are common in newborns whose mothers have received high-dose pyridoxine therapy for hyperemesis gravidarum.

Step VI. Maintenance anticonvulsant therapy with Phenobarbitone (3–6 mg/kg/day q12h) or Phenytoin (4–8 mg/kg/day q12h) or Levetiracetam 40 mg/kg/day q12h for 6–8 weeks is necessary in all non-metabolic seizures, the choice depending on the response in bolus therapy. Maintenance therapy should be started after 24 hours of last bolus dose. Unlike adults, prolonged anticonvulsant therapy is not required in most newborns due to little risk of recurrence in neonatal seizures and significant side effects on growth and development.

Specific therapy is needed for primary disease, e.g. meningitis, narcotic withdrawal, etc. apart from anticonvulsants.

Outcome of neonatal seizures depends on primary cause, though ~ 10–20% of untreated convulsing infants may die due to asphyxia and choking. Risk of long-term neurological deficit depends on the primary cause, though high-risk factors include—(a) onset of seizures on first day of life, (b) persistence beyond 48 hours despite anticonvulsant therapy and (c) myoclonic seizures. *Metabolic seizures have best prognosis with very rare long-term neurological damage.*

12.17 HEMATOLOGICAL DISORDERS IN NEWBORN

Hematological status *at birth* is characterized by:

- Higher hemoglobin levels (~14–16 gm/dl) with predominance of HbF (~70%),
- Higher reticulocyte count (>5%), suggestive of rapid bone marrow turnover,
- Higher TLC (~18,000 cells/mm^3), with lymphocytic predominance (>60%), and
- Relative thrombocytopenia with immature hemostatic mechanisms. All clotting factors are low in newborns except factor $_f$V, VIIIs and XIII as also Antithrombin III, plasminogen and protein-C levels.

These developmental features change rapidly in neonatal period to reach adult values and should always be considered while assessing a neonatal blood reports. This chapter deals with common hematological problems in newborns, i.e. bleeding, anemia and polycythemia.

12.17.1 BLEEDING NEONATE

Newborns are prone for bleeding tendencies due to: (a) developmental thrombocytopenia, (b) developmental deficiencies of clotting factors, (c) vitamin K deficiency

due to inadequate endogenous synthesis by immature gut flora, and (d) higher vascular permeability. Coagulation proteins do not cross placenta and synthesized in fetus from 10th week of gestation.

Etiology: Bleeding problems in newborn vary from mild/moderate bleeds in an apparently healthy child, e.g. *hemorrhagic disease of newborn* (HDN), to life-threatening hemorrhage, e.g. DIC in critically sick babies **(Table 12.52)**.

Diagnostic approach: A bleeding newborn may bleed *externally* from umbilical cord, skin, gastrointestinal; tract and IV sites etc; or *internally*, e.g. intracranial hemorrhage. Severity of clinical signs depends on the site and severity of bleed as well as primary cause.

Important diagnostic clue include:

- ***Detailed history,*** with special reference to:
  - Age of onset **(Table 12.53)**
  - Family history of bleeding disorders
  - Antenatal maternal infections
  - Obstetric complications, e.g. APH (swallow-blood),
  - Postnatal feeding, (e.g. HDN in breastfeds)
- ***Clinical examination,*** with special reference to:
  - *General appearance*: term and healthy (HDN) or preterm and sick (DIC).
  - *Site of bleed*: IV sites (DIC), cord (slipped ligature, hemophilia), vagina (withdrawal bleeding, HDN).
  - Associated sepsis, asphyxia, hypothermia (DIC).
  - Hepatosplenomegaly (IU infections).

  Signs of concealed/internal bleeding, e.g. *progressive pallor, deep icterus, and shock* are rare in classic HDN and usually indicate more severe etiology.
- ***Laboratory investigations:*** Need for investigations **(Table 12.54)** depends on severity of bleed and probable etiology.

No investigations are necessary in healthy breastfed term newborn with minor bleeding, who has not received vitamin K at birth and responds rapidly to single dose of vitamin K (suggestive of HDN).

Apt and Downey test is used to distinguish swallowed maternal blood from fetal blood in babies with blood mixed vomiting/melena. Mix 1 part of vomitus/stool with 5 parts of distilled water > centrifuge > add 1 ml of 1% NaOH > a change of color to yellowish-brown indicates swallowed maternal blood, due to denaturation of adult Hb. Fetal Hb is resistant to alkali denaturation.

A step-wise approach is preferred in other cases, beginning with three base-line investigations: (a) platelet count, (b) prothrombin time, and (c) partial thromboplastin time; to differentiate common causes of bleeding neonate **(Table 12.55)**. Detailed investigations may be necessary to confirm the diagnosis or detect uncommon defects.

TABLE 12.52: Causes of bleeding neonate

- **Coagulation disorders**
  - Hemorrhagic disease of newborn (HDN)
  - *Inherited:* hemophilia, von-Willebrand disease
  - *Hepatic injury:* hypoxia, infections
  - *Maternal drugs:* anticoagulants, salicylate, phenytoin
- **Platelet disorders (purpura)**
  - *Increased destruction:*
    - *Immunological:* Neonatal ITP
    - *Mechanical:* Hemagioma, NEC
  - *Decreased bone marrow production:*
    - BM depression—infections, hypoxia, drugs
    - BM infiltration—leukemia, Gaucher disease
  - *Hereditary disorders:*
    - Wiskott-Aldrich syndrome
    - Function defects—Glanzmann thrombasthenia
- **Vascular immaturity/injury**
  - Intra-ventricular hemorrhage
  - *Trauma:* Birth trauma, slipped cord ligature
- **Disseminated intravascular coagulation (DIC)**
- **Swallowed maternal blood**

TABLE 12.53: Causes of N. bleeding with age of onset

<24 hour	:	Swallow' blood, *early HDN*, hemophilia
>24–72 hour	:	*Classic HDN*, DIC, neonatal ITP
>72 hour	:	Sepsis, hypoxia/acidosis, DIC, IU infections
>7 day	:	*Late HDN*, inherited clotting disorders

TABLE 12.54: Lab. investigations in bleeding neonate

Step I. Baseline investigations

- Apt test (swallowed blood)
- Platelet count (thrombocytopenia)
- Peripheral smear (sepsis, leukemia)
- Basic clotting profile (BT, CT, PT, PTT)

Step II. Relevant investigations

- Platelet function tests
- Clotting factor assays
- FDP or D-dimer assay (DIC)
- Maternal platelet count (for neonatal ITP)
- Coomb test (platelet isoimmunization)
- Liver function tests

TABLE 12.55: Diagnostic approach to bleeding neonate

Plc	*PT*	*PTT*	*Diagnosis*
		Clinically well neonate	
N	N	N	Trauma, platelet function defects
N	N	↑	Inherited clotting factor deficiency
N	↑	↑	Hemolytic disease of newborn
↓	N	N	Immune thrombocytopenia (ITP)
		Clinically sick neonate	
N	N	N	Vascular purpura*
N	↑	↑	Liver disease, heparinization
↓	N	N	Mechanical purpura**
↓	↓	↓	DIC

Plc: Platelet count. *e.g. in preterms, acidosis, asphyxia
**excessive platelet destruction, e.g. in sepsis, NEC, hemangioma

Hemorrhagic disease of newborn (HDN) is the commonest cause of bleeding in newborns, due to transient *Vitamin K deficiency*—required for synthesis of coagulation factors—II, VII, IX and X. The term ***Vitamin K deficiency bleeding*** **(VKDB)** is preferred by some workers, as HDN is not limited to newborns and neonates may bleed due to other causes rather than vitamin K deficiency.

According to the age of presentation and etiology, HDN may be divided into 3 types:

a. **Classical HDN,** manifests on 2–7th day and almost exclusively seen in full-term breastfed newborns with estimated incidence of ~0.5–1.0%.

   Etiologically, it is linked to—(i) marginal vitamin K content in breast milk, (ii) delayed/inadequate feeding, and (iii) inadequate endogenous vitamin K synthesis due to relatively sterile gut.

   Clinically, these newborns are apparently healthy, except mild bleeding from superficial sites, e.g. umbilical stump, nose, vagina, venepunctures, circumcision wounds, etc. Mild transient gastrointestinal bleeding is not uncommon but serious intracranial bleeds are very rare.

b. **Early HDN** presents with severe bleeding manifestations within 24 hours of birth, due to vitamin K deficiency following maternal therapy with drugs that interfere with vitamin K metabolism, e.g. anticoagulants, anticonvulsants, antitubercular drugs and salicylates.

c. **Late HDN** presents beyond 1st week of life (usually 3–8th week) due to inadequate endogenous synthesis in gut, usually in *sick babies* with cholestatic liver disease, malabsorption syndromes and prolonged antibiotic therapy, when normal gut flora is destroyed. Unlike classic disease, serious internal bleeding and intracranial hemorrhage is common.

Diagnosis of classical HDN is largely clinical (bleeding in apparently healthy newborn), supported by abnormal coagulation profile and therapeutic response to vitamin K within 30–120 minutes.

In early/late HDN, diagnosis may be confirmed by *elevated PIVKA-II levels* (proteins induced in vitamin K absence).Vitamin K levels are difficult to measure and unreliable.

Management: A single dose IV or SC vitamin K_1 (1–5 mg) is the treatment of choice for VKDB/HDN, even before laboratory confirmation. IM injections should be avoided due to risk of large hematoma formation. Severe or persistent bleeding may require repeated doses along with factor replacement therapy with fresh frozen plasma (10 ml/kg) or prothrombin complex concentrates.

Late VKDB is a chronic problem and may need regular vitamin K supplements (1 mg/months IM *or* 50–100 mg/day PO) as well as treatment of primary cause.

Prevention: Prophylactic administration of a *single dose of IM vitamin K 1mg* (0.5 mg in babies weighing < 1000 gm) at birth is an established practice to prevent almost all cases of classic/Late HDN. While oral vitamin K prophylaxis is equally effective to prevent classic HDN in fullterms, protection is inadequate against late HDN. Infants on antibiotics for > 2 weeks should receive 0.5 mg vit K per week.

Pregnant mothers on oral anticonvulsants should receive daily vitamin K supplements (PO 10–20 mg) for 15–30 days before delivery to prevent early HDN.

12.17.2 ANEMIA IN NEWBORN

Considering developmentally higher hemoglobin levels in normal newborn, neonatal anemia is defined as *Hb <13 gm in fullterm and <12 gm/dl in preterms, during first two weeks of life.*

Etiology: Transplacental iron transfer is an active process, not affected by maternal Hb levels and maternal anemia is unlikely to cause neonatal anemia. however, since maximum iron transfer through placenta occurs in last trimester, preterms are anemic.

Rh/ABO incompatibility, perinatal blood loss and *sepsis* are three most important causes of anemia in newborn, apart from others **(Table 12.56)**. Repeated blood sampling is an important cause of severe anemia in neonatal intensive care.

Fetomaternal hemorrhage, though occurs in ~50% pregnancies, is rarely enough to cause significant neonatal anemia (<1%).

Clinical evaluation of neonatal anemia includes:

- Family history of hereditary hemolytic anemia
- Maternal blood group (Rh/ABO incompatibility)
- Prenatal history of infections or invasive procedures
- History of multiple pregnancy (twin-twin transfusion) and cord clamping time.
- *Co-existing problems:* Cephalohematoma, severe edema (hydrops), hepatosplenomegaly, icterus, sepsis, etc.

TABLE 12.56: Causes of severe anemia in newborn

Increased blood loss
- *Fetal:* Feto-fetal or feto-maternal hemorrhage
- *Placental:* Placenta previa. antepartum hemorrrhage
- *Cord:* Early/late clamping, trauma, anomalies.
- *Birth injuries:* Cephalohematoma
- Bleeding neonate

Increased RBC destruction
- Hemolytic disease of newborn (Rh/ABO)
- Congenital hemolytic anemia
- *Acquired hemolysis:* Sepsis, IU infections, drugs

Decreased RBC synthesis
- Anemia of prematurity
- *Bone marrow hypoplasia:* Drugs, IU Infection
- *Bone marrow infiltration:* Leukemia, osteopetrosis

Iatrogenic
- Repeated blood sampling
- Post-exchange (low Hb content in adult blood)

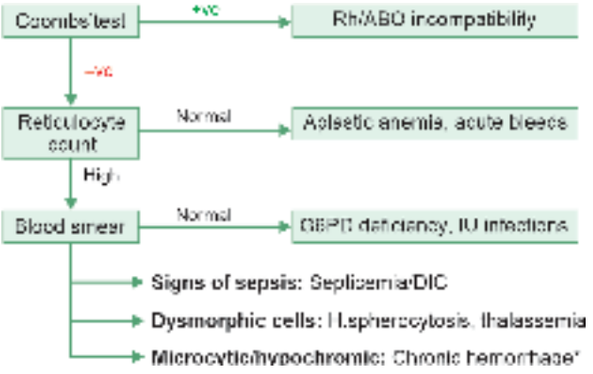


Fig. 12.24: Diagnostic algorithm for neonatal anemia.
*exclude feto-maternal or twin-twin transfusion (Kleihauer test)

Laboratory evaluation: **Fig. 12.24** provided a practical algorithm for laboratory diagnosis of neonatal anemia, though common investigations include:

- Complete hemogram including Hb, Hct, cell counts and Reticulocyte count
- P. smear for hemolysis, sepsis, abnormal cells
- Direct Coombs' test (Rh/ABO disease)
- Sepsis screen, including relevant cultures
- Serological tests for intrauterine infections
- Bone marrow examination (in selected cases)
- Coagulation profile (in bleeding disorders)
- *Kleinhauer test*

Kleihauer-Betke test is used to detect presence of fetal RBCs in maternal blood in fetomaternal hemorrhage, as follows:

Collect maternal smear along with controls from a normal newborn and adult > Fix them with 80% ethanol for 5 minutes > Rinse, dry and immerse in a buffer solution (73.4% of 0.1 M citric acid + 26.6% of 0.2 M disodium hydrogen phosphate) for 5 minutes > Hematoxylin-eosin staining > Examine under microscope. On microscopy, RBCs with acid-resistant fetal Hb remain darkly stained, while those with adult Hb appear like ghost cells, due to acid elution. *Presence of ~ 1% of fetal RBCs in maternal smear indicates ~ 50 ml of fetal blood loss to maternal side.*

Management of neonatal anemia depends on its severity, primary cause and associated problems. Packed RBC transfusion (15 ml/kg over 2–4 hours) is indicated according to the hemoglobin levels and clinical status of the newborn as follows:

- On mechanical ventilation @ Hb < 11 gm/dl
- On minimum respiratory support @ Hb < 10 gm/dl
- On oxygen or impending CCF @ Hb < 8 gm/dl
- Asymptomatic newborn @ Hb < 7 gm/dl

Anemia of prematurity may be prevented with recombinant *erythropoietin* therapy (25–100 U/kg SC alternate day) with PO iron (2 mg/kg/d) from 2nd week onwards, though rarely practiced.

12.17.3 NEONATAL POLYCYTHEMIA

Polycythemia (Hct >65%) is seen in ~1% of newborns, specially full-terms with following risk factors:

- Delayed clamping of cord,
- Twin-twin transfusion in recipient baby,
- Infants of diabetic mother,
- Cyanotic CHDs (compensatory) *or rarely in,*
- Endocrinal disorders, e.g. cong. adrenal hyperplasia,
- Chromosomal disorders, e.g. Down syndrome.

Pathophysiologically, it leads to increased blood viscosity (thromboembolic episodes), volume overload (CCF) and increased metabolic requirements for cell survival (hypoglycemia, hypocalcemia).

Clinically, visible plethora is the only indicator of polycythemia in most babies, though severe cases may develop complications, e.g. CCF, hypoglycemia, hypocalcemia and seizures.

Management: *Plasma exchange* is treatment of choice in cases with Hct >70, with an aim to bring it <55. Exchange volume may be calculated as

(Observed Hct – 55/observed Hct) × 85 × Weight (kg).
where 55 is desired Hct and 85 is blood volume/Kg.

12.18 METABOLIC DISORDERS IN NEWBORN

Some important metabolic problems in newborns are as follows:

Hypoglycemia is the commonest metabolic problem in newborn, generally defined as *blood glucose (BG) values of <25 mg/dl during first 3 hours, <35 mg/dl between 3 and 24 hours and <45 mg/dl beyond the first day,* irrespective of gestation or birth weight. BG levels of 45 mg/dl may be considered as cut-off for hypoglycaemia in symptomatic newborns.

However, there is lack of consensus on cut-off BG value and current practice is based on operational thresholds for intervention, i.e. BG should be maintained >60 mg/dl in symptomatic neonates after 48 hrs of life.

Etiology: Normal fetal glucose levels are ~2/3rd of maternal values, which drop further during first two hours before rising again to normalize by 3–4 hours of age. Poor fetal reserves in preterm/LBW babies and delayed feeding are two most common causes of neonatal hypoglycemia **(Table 12.57)**.

TABLE 12.57: Risk-factors for neonatal hypoglycemia

- Preterms, low birth weight and IUGR
- Large for date or post-term newborns
- Infants of diabetic mother (IDM)
- Delayed or inadequate feeding
- Rh-incompatibility and exchange transfusion
- *Critical illness:* Polycythemia, sepsis, hypothermia
- Inborn errors of metabolism (rare)

Clinical manifestations of hypoglycemia not necessarily correlate with blood glucose level. Most cases present on 2nd–3rd day with:

- *Abnormal movements*, e.g. jitteriness, tremors or seizures,
- *Abnormal behavior*, e.g. apathy, limpness, refusal to feeds and coma,
- *Autonomic disturbances*, e.g. recurrent apnea, tachycardia, sudden pallor, sweating, etc.

Diagnosis rests *low blood glucose levels*, preferably from laboratory. *Dextrostix*, while adequate for screening, are not reliable at very low glucose levels.

Prevention of hypoglycemia includes: (a) early breastfeeding, (b) routine glucose monitoring in high-risk newborns at 2,6,12, 24, 48 and 72 hours, and (c) prevention/ treatment of precipitating factors, e.g. hypothermia, sepsis, etc.

Routine BG monitoring is recommended for all preterms < 35 weeks, LBW < 2000 gm, infant of diabetic mothers, large-for-date babies and sick newborns.

Management depends on the severity of hypoglycemia as follows:

- ***Symptomatic hypoglycemia or BG levels < 20 mg/dl*** irrespective of symptoms, need IV bolus of Dextrose 10%, followed by slow infusion of 6–12 mg/kg/min to maintain BG levels >45 mg/dl for at least 24 hours before tapering slowly under monitoring and simultaneously ensuring oral feeds.
- ***Asymptomatic hypoglycemia with BG >20 mg/dl*** does not need urgent correction and treated with adequate feeding and additional sugar-fortified feeds, if necessary. However, BG must be reassessed after 30 minutes and must be treated with IV Dextrose 10%, if remains <40 mg/dl.
- ***Refractory hypoglycemia,*** defined as failure to maintain normal BG levels despite 12 mg/kg/min of Dextrose 10% infusion for 48 hours must be investigated for endocrinal disorders, (e.g. adrenal insufficiency), hyperinsulinemic states, (e.g. Islet cell hyperplasia) and inborn errors of metabolism, (e.g. glycogen storage disorders). Some of them may benefit with IV hydrocortisone (5 mg/kg), IV Glucagon (300 mg/kg) or IV Diazoxide (25 mg/kg/d q8hr) therapy. Glucagon is more useful in high-insulin hypoglycemia, e.g. infants of diabetic mothers and hemolytic disease of newborn.

Outcome: Untreated symptomatic hypoglycemia may be fatal, though timely intervention ensures dramatic recovery. Persistent hypoglycemia in newborn may leave neurodevelopmental problems in 30–70% cases.

Hypocalcemia is second commonest metabolic disorder in newborns, defined as *S. calcium <7 mg/dl in preterms and <8 mg/dl in term newborns or ionic fraction < 4 mg/dl.*

TABLE 12.58: Causes of neonatal hypocalcaemia

- **Early-onset *(with 24–72 hours)***
  - Preterms and VLBWs
  - Infants of diabetic mothers
  - Perinatal complications, e.g. prolonged labor
  - Maternal medications, e.g. nifedipine
- **Late-onset *(classic tetany)***
  - Formula-fed newborn (wrong Ca:P ratio)
  - Iatrogenic—ET, rapid acidosis correction
  - Maternal hyperparathyroidism
  - Hypoparathyroidism, e.g. DiGeorge syndrome

ET: Exchange transfusion

Etiology of hypocalcemia differs with age of presentation **(Table 12.58)**.

- *Early-onset hypocalcemia* (<72 hour) is common in preterms due to poor storage and immature renal functions to conserve calcium.
- *Late-onset hypocalcemia* is common in formula-fed newborns, due to high phosphorus content that prevents calcium absorption.

Clinical features of hypocalcemia include:

- *Seizures*, usually on 3rd day, in otherwise alert and active newborn,
- *Neuromuscular irritability*, e.g. jitteriness, sustained clonus and high-pitched cry. Well-defined tetany is uncommon in newborns.

Diagnosis depends on S. Calcium levels including ionic fraction, drawn before the therapy and therapeutic response to IV calcium infusion. Parathyroid studies are indicated in refractory hypocalcemia.

Management of hypocalcemia includes:

- ***Symptomatic cases*** should be treated by IV Calcium gluconate 10%, 2 ml/kg (half-diluted in DW 5%), infused slowly at the rate of <1 ml/min with cardiac monitoring for bradycardia. Maximum dose is 10 ml in term newborns and 5 ml in preterms. Post-bolus, a maintenance dose of 2 mg/kg 6-hrly must be continued for next 24–48 hours, before switch-over on oral maintenance. IV site should also be observed for extravasation.
- ***Asymptomatic hypocalcemia*** *or* symptomatic cases after initial therapy as above, should receive oral elemental calcium supplements as 40–80 mg/kg/d for next 3 days.
- ***Unresponsive hypocalcemia*** may be associated with hypomagnesemia, which needs to be corrected along with calcium therapy (as discussed below).

Outcome is excellent in hypocalcemic seizures, with no neurodevelopmental sequelae, unless due to primary cause.

Hypomagnesemia, defined as serum magnesium levels *< 1.2 mEq/L*, is relatively uncommon, usually seen along

with hypocalcemia in IUGR babies, infants of diabetic mothers and after diarrhea.

Clinically Hypomagnesemia *per se* rarely produces seizures, but in its presence, hypocalcemic seizures do not respond to calcium therapy.

Treatment includes IM magnesium sulphate 50% (0.2 ml/kg), two doses at 12-hour interval, followed by oral supplements (30 mg/d) for 3–5 days.

Late metabolic acidosis is common in top-fed preterms (5–10%), due to high solute load in formula milks and immature renal acidification.

Clinically, these cases present in 2nd–3rd week, with failure to thrive, tachypnea without lung signs, circumoral pallor and sluggish activity.

Diagnosis rests on blood gas analysis showing: (a) persistent metabolic acidosis, (b) increased anion gap, (c) normal/low pCO_2, and (d) base excess <5 mmol/L.

Treatment includes oral $NaHCO_3$ therapy for 2 weeks or till 35 weeks of conceptional maturity, with suitable modifications in formula-feeds.

Infant of diabetic mother (IDM): Diabetes mellitus, including gestational diabetes, is the commonest metabolic disorder in pregnancy with significant effects of fetal outcome.

Pathological effect on fetus: Hyperglycemic state in mother leads to fetal hyperglycemia with compensatory rise in fetal insulin levels and islet cell hyperplasia. In presence of fetal hyperglycemia, insulin acts as an anabolic hormone-leading to *macrosomia*. Post-birth, with sudden cut-off of transplacental glucose supply, this high insulin-state may precipitate *severe hypoglycaemia in early neonatal period*.

Clinically IDMs present with:

- *Typical physical features*, i.e. macrosomia, moon facies, hypertrichosis and hairy pinna.
- *Complications*, e.g.
  - Obstructed labor and birth trauma due to large size,
  - Hypoglycemia and hypocalcemia (on 2nd–3rd day),
  - Hyaline membrane disease (surfactant maturity),
  - Polycythemia, leading to hyperbilirubinemia and renal vein thrombosis.

Congenital malformations, e.g. CHDs (specially asymmetric septal hypertrophy), neural tube defects and small left-colon syndrome, are also common in IDMs.

Management of IDMs include:

- ***Antenatal management:*** Oral hypoglycemic agents are contraindicated in pregnancy due to teratogenic effects and intractable hypoglycemia in newborn and near-normoglycemic state should be maintained with insulin. Periodic monitoring of amniotic fluid surfactant activity by L:S ratio is advised to ensure adequate maturity at birth.
- ***Obstetrical care:*** Planned delivery is preferable in most cases and those with large fetal size may be taken for elective caesarean section.
- ***Postnatal management*** includes: (a) early feeding within 30 minutes to prevent hypoglycemia, (b) glucose monitoring at 2, 6, 12, 24, 48 and 72 hours, (c) detection and treatment of hypoglycemia as well as other complications, e.g. HMD, polycythemia, hyperbilirubinemia and other metabolic disturbances, and (d) management of co-existing malformations, e.g. cardiac disease. All IDMs with respiratory distress must undergo echocardiography to exclude asymmetric septal hypertrophy.

12.19 CONGENITAL MALFORMATIONS

Congenital malformations are defined as "*anatomical or structural defects, present at birth, with/without functional impairment*." Although used interchangeably, the term congenital anomaly has wider connotation, i.e. *structural, functional, biochemical or physiological disorders of prenatal origin*.

Structural malformations may be broadly divided into *major malformations* with significant functional impairment, e.g. CHDs or neural tube defects; and *minor malformations* without direct functional implications, e.g. pre-auricular skin tags.

Incidence: Congenital malformations are third commonest cause of perinatal mortality in India, estimated to be present in ~2.5% of newborns at birth and incidence may rise to 4–5% by 5 years, as many defects manifest in later life.

Etiology: Over 60% of congenital malformations are idiopathic, rest due to various intrinsic (genetic) defects or extrinsic (environmental) factors **(Table 12.59)**. Term *teratogens* is applied to those environmental influences, which are known to have definite exposure-risk relationship with a congenital anomaly, e.g. maternal infections, drugs, radiation and alcohol/ smoking. Only 10% malformations are due to recognizable teratogens.

Classification: Congenital malformations may be single primary defects or multiple malformation syndromes.

TABLE 12.59: Common causes of congenital malformations

- **Idiopathic (~60%)**
- **Intrinsic or inherited (~ 25–30%)**
  - *Chromosomal:* Down syndrome, Turner syndrome
  - *Single gene:* Achondroplasia, Holt-Oram syndrome
  - *Polygenic:* Cleft palate, neural tube defects, CHDs
- **Extrinsic *or environmental* (~10–15%)**
  - *Maternal infections:* Rubella, CMV, toxoplasmosis
  - *Maternal diseases:* Diabetes, iodine deficiency
  - *Drugs/toxins:* Antiepileptics, alcohol, hormones
  - *Maternal smoking, irradiation*
  - *Maternal malnutrition,* e.g. folic acid deficiency
  - *Uterine anomalies or oligohydramnios*

Depending on the etiology and secondary effects, various terms are used to denote these defects, as follows:

- **Malformation,** i.e. a single morphological defect due to intrinsic error in embryogenesis and organ differentiation, e.g. cleft lip or CHD.
- **Deformation,** i.e. abnormal shape/position of normally-formed body part due to abnormal uterine pressure/posture, e.g. congenital dislocation of hip or congenital talipes equinovarus. Abnormal posture may be due to extrinsic uterine pressure, e.g. *oligohydramnios*, or intrinsic fetal hypotonia, e.g. *neuromuscular disorders*.
- **Disruption,** i.e. destruction of a normally-formed body part in late gestation, due to: (a) tearing/amputation of a structure by floating strands of amnion, e.g. amniotic band syndrome, loss of a digit or limb, etc.; or (b) interruption of blood supply due to infection, trauma or other teratogens, leading to distal infarct, necrosis or resorption, e.g. intestinal atresia, porencephaly, etc.
- **Dysplasia** denotes abnormal organization of constituent cells in a structure, leading to abnormal growth. Dysplasias may be *localized*, e.g. hemangioma, or *generalized*, e.g. skeletal dysplasia. Being growth-dependent, clinical appearance in these defects tend to change with age, e.g. hemangiomas may regress or skeletal dysplasias may deteriorate, postnatally.
- **Sequence** denotes a spectrum of multiple malformations due to cascading effect of a single primary defect in morphogenesis. Depending on the primary error, a sequence is further classified as malformation, deformation or disruption sequence. Some common sequences include:
  - *Robin malformation sequence,* with primary defect of mandibular hypoplasia, leading to macroglossia, glossoptosis and high-arched palate.
  - *Breech deformation sequence* due to abnormal uterine pressure in breech position, leading to abnormal skull shape, facial asymmetry, torticollis, CDH and CTEV. Similar abnormalities are also seen *Potter's sequence,* due to oligohydramnios.
  - *Amniotic band disruption sequence*, due to disruption of normally formed amniotic membrane, leading to defects, e.g. cleft lip, limb defects, aplasia cutis, etc. Sequences need to be differentiated from multiple malformation syndrome, as the recurrence risk in them depends on the primary defect.
- **Multiple malformation syndrome** denotes presence of one or more development abnormality involving at least two different systems, due to an established cause. Most of these defects are chromosomal or polygenic in origin, e.g. Down syndrome, though others may be due to single gene defects or environmental factors, e.g. intrauterine exposure to infection/drugs (congenital rubella syndrome, fetal hydantoin syndrome, etc.).
- **Association** denotes a non-random (more than by chance) occurrence of multiple malformations in a combination, not explained by a common etiological basis, i.e. syndrome or sequence. Two common associations are:
  - *VATER association* (***V***ertebral anomalies, ***A***nal atresia, ***T***racheoesophageal fistula, ***E***sophageal atresia and ***R***enal/Radial defects).
  - *CHARGE association* (***C***oloboma, ***H***eart disease, Choanal ***A***tresia, growth/mental ***R***etardation with/without CNS anomalies, hypo***G***onadism and ***E***ar anomalies or deafness.

TABLE 12.60: Diagnostic clues for congenital malformations

History
- Family history of malformed parents/sibling
- Parental consanguinity
- Elderly mother or father
- *Teratogens:* Infections, drugs, alcohol
- Maternal diseases, e.g. diabetes
- Oligo-/poly-hydramnios
- Abnormal fetal movements/presentation

Clinical examination
- External appearance
- Patency test/orifice count at birth
- Single umbilical artery
- Stigmata, e.g. spinal hair tuft, auricular tags
- Systemic examination, e.g. CHDs

Diagnosis: Although most congenital malformations are obvious at birth, some may be easily missed in early life. Early diagnosis of major malformations is essential for survival, appropriate management and prevention of late complications. Important clinical clues about presence of a congenital malformation or etiological diagnosis are given in **Table 12.60**, though confirmation may require relevant investigations. Genetic studies are indicated in select cases with intrinsic cause of malformation, to assess the risk of recurrence and prenatal diagnosis. Diagnosis and management of individual congenital malformations has been discussed in related chapters.

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CHAPTER 13

Adolescence and Adolescence Disorders

Surbhi Rathi, Mukesh Agrawal

Adolescence is a period of transition from childhood to adulthood with many physical, physiological and psychological changes.

WHO defines *Adolescence* from 10–19 years of age, which may be arbitrarily divided into 3 phases—early adolescence (10–13 years), mid adolescence (14–16 years) and late adolescence (17–19 years). While *Early adolescence* is a period of rapid physical and sexual growth, *mid-adolescence* is characterized by relative slowing of growth spurt but intense emotional changes to develop self-identity. *Late adolescence* marks the completion of physical growth and psychosocial stabilization.

13.1 ADOLESCENT GROWTH AND DEVELOPMENT

Adolescence is a period of: (a) physical growth spurt, (b) sexual maturity (puberty), and (c) marked behavioral or psychological change. A general sequence of important physical and pubertal events during adolescence is illustrated in **Fig. 13.1**, though some important details are as follows:

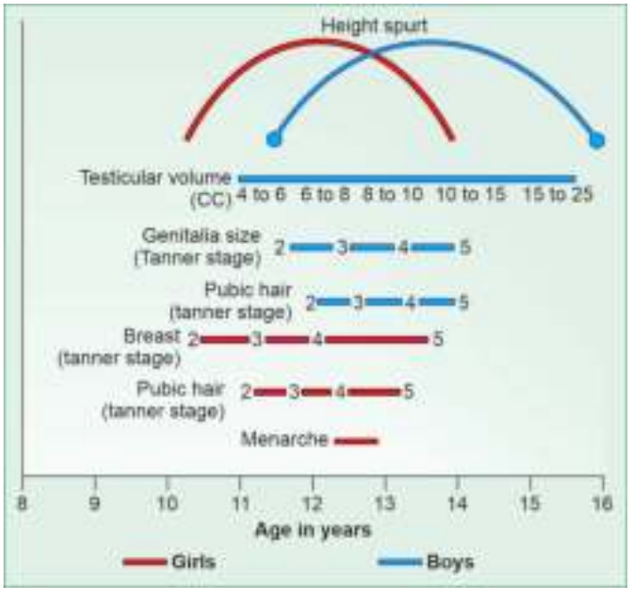

Fig. 13.1: Chronology of pubertal changes.

I. Physical growth: Adolescent growth spurt begins with gradual increase in height velocity, followed by rapid weight gain in both sexes. Important characteristics of physical or somatic growth during adolescence are:

- *Earliest physical change in adolescence is the linear (height) growth spurt*, which begins, peaks and ends earlier in girls than in boys **(Table 13.1)**, as testosterone is a weaker stimulant of growth hormone than estrogens. This spurt is asymmetrical in initial years of puberty, being more prominent in distal parts, e.g. limbs, giving a tall, thin and gawky appearance to adolescents.
- *Peak height velocity* (PHV) in girls is reached earlier than in boys during SMR stage III (discussed later) and *precedes* menarche by 1–1.5 years. In boys, PHV is reached later in SMR stage IV.
- *Rapid weight gain* begins later than the linear growth spurt. An adolescent gains 4–4.5 kg/year, compared to 2–3 kg/year in post-infancy childhood. The distribution of weight gain also differs in two sexes-predominant muscular growth in boys and predominantly fat deposition in girls. Consequently, the lean body mass, which is ~80% in prepubescent children, increases in boys to ~90% and decreases in girls to ~70%.
- *Skeletal growth* is more advanced in girls. In both sexes, bone age correlates better with sexual maturity than chronological age.
- *Other* important physical growth characteristics during adolescence are laryngeal enlargement with voice changes and elongation of optic globe with consequent myopia in some cases.

TABLE 13.1: Linear growth spurt in adolescence

	Males	*Females*
Age of onset	11 years	9 years
Age of PHV	14 years	12 years
Age of completion	18 years	15 years
Total height gain	28 cm	26 cm
Max PHV (per year)	10.5 cm	9 cm

PHV: Peak height velocity. All approximate values

II. Sexual maturity is the hallmark of adolescence, also referred as puberty, i.e. a series of biological changes that lead to development of reproductive capacity and involves development of *primary* (testicular and penile growth in boys and breast and uterine growth in girls) and *secondary* sexual characteristics (pubic and axillary hair, body odor, voice changes, etc.).

While age of the onset and completion of puberty has significant individual variations due to familial, genetic and environmental factors, the sequence of pubertal changes is fairly consistent, usually assessed by ***Tanner's sexual maturity rating*** (SMR) **(Table 13.2)**. Important events in sexual maturity are as follows:

In girls, the first visible sign of puberty is *Thelarche*, i.e. appearance of breast buds at ~11 years (8–13 years), followed by *adrenarche*, i.e. appearance of fine, straight pubic hairs.

Average age of menarche in Indian affluent girls is ~12.5 years (10–16 years), i.e. after ~ 2–2.5 years of thelarche. PHV precedes menarche by 1–1.5 years, i.e. during SMR stage III.

Important genital changes in girls during puberty are: (a) enlargement of external/internal genitals, (b) start of ovulation after 1–1.5 years of menstruation, (c) vaginal mucosal changes, e.g. thickening, glycogen accumulation and increased secretions from Bartholin glands (*physiological leucorrhoea*).

In boys, first visible sign of puberty is the *increase in testicular size* at ~11.5 years (9–14 years), followed by adrenarche and penile enlargement. PHV in boys usually occur late in SMR stage IV.

Important genital changes in boys during puberty are: (a) increase in the testicular volume from ~4 ml in pre-pubertal age to ~20–25 ml by the completion of puberty, (b) effective sperm secretion (*spermarche*) at any time after ~12 years of age, and (c) penile enlargement beginning after ~1 year of starting the testicular growth and continuing till the end of puberty, though final size gain may vary individually.

III. Behavioral changes: Adolescence is a period of intense psychological and emotional turmoil, characterized by identity formation, including development of sexual identity. Important behavioral changes during different phases of adolescence include:

- ***Early adolescence*** is characterized by the preoccupation with body image and pubertal changes along with concrete thinking, i.e. literal perception of concepts and impulsivity with disregard to future implications. Sexual fantasies are common.
- ***Mid adolescence*** is characterised by peer-influence and family/social conflicts to develop self-identity. Risk-taking behavior is common including experiences, e.g. smoking, drinking and sexual actions, to display newly discovered autonomy. Abstract reasoning, to some extent, begins in this phase. This phase is also characterized by formation of sexual orientation and sexual identity.
- ***Late adolescence*** is a phase of stabilization with conflict resolutions with family/society, lessening of impulsivity and peer pressure, development of personal carrier goals and establishment of sexual identity.

Behavioral changes are most prominent during mid-adolescence and gradually culminate into development of stable body image, functional independence, consolidation of sexual identity and stable relationships. Inability to cope with these changes is responsible for behavioral disorders and social maladjustments in youth, discussed later.

13.2 COMMON HEALTH PROBLEMS IN ADOLESCENCE

Adolescence is not only a period of peak physical activity, hormonal changes and emotional stress, but also of heightened concern about body image. Consequently, many health problems present *or* noticed first time in this age group, apart from age-unrelated illnesses **(Table 13.3)**.

TABLE 13.2: Tanner's sexual maturity rating

	(Boys)			*(Girls)*	
Stage	***Testes/Scrotum***	***Penis***	***Pubic hair***	***Breast***	***Pubic hair***
I	Preadolescent	Preadolescent	None	Preadolescent	Preadolescent
II	↑ size, rugosities	↑ size	Scanty, straight, light	Primary mound*	Sparse, light, straight on medial side of labia
III	Larger	Larger	Darker and curlier	↑ areola diameter No separate contour	Darker, curlier
IV	Larger, darker	Thicker, ↑ glans size	Coarse, adult type not on thighs	Secondary mound**	Coarse, curly, not on thighs
V	Adult size	Adult size	On medial thigh	Mature, nipple projects	Adult feminine triangle, spread on medial thighs

*elevated breast/papilla. **areola/papilla with separate contour

TABLE 13.3: Common health problems in adolescence

Developmental disorders
- Delayed/precocious puberty
- Short/tall stature

Physical disorders
- Physiological obesity
- *Nutritional:* Undernutrition, anemia, goiter
- *Skin:* Acne, Hirsutism
- *Orthopedic:* Sports injuries
- *Systemic:* Asthma, hypertension, diabetes
- Accidents

Breast problems
- Physiological asymmetry
- Delayed/premature thelarche
- Gynecomastia
- Breast masses or hypertrophy
- Nipple discharge
- Missed congenital anomalies

Menstrual problems
- Physiological irregularities
- Delayed/premature menarche
- Ammenorrhea/dysmenorrhea
- Abnormal or dysfunctional uterine bleeding

Urogenital problems
- Physiological variations
- Leucorrhoea
- Perineal or peri-genital infections
- Sexually transmitted diseases
- Urinary tract infections
- Missed congenital anomalies

Psychosocial/emotional disorders
- *Adaptive:* Depression, suicide, delinquency
- *Somatic:* Anorexia nervosa, bulimia, hysteria
- *Psychosexual:* Masturbation
- *Social:* Substance abuse, teen pregnancy

A. Developmental disorders: Achievement of *puberty* is the essence of development in adolescence, due to sequence of hormonal changes over time (Ch 22.6.2, **Fig. 22.6)**.

Delayed or precocious onset of pubertal changes is a common cause of medical consultations during adolescence. As most of these variations are familial, detailed parental history, specially regarding their pubertal events, is essential to differentiate normal variants from potentially disease states.

Precocious puberty (PP) is defined as:
- Appearance of secondary sexual characteristics before 8 years in girls and 9 years in boys; or
- Onset of menarche before 10 years, in girls.

Precocious puberty may be *central* in origin-due to premature activation of hypothalamic-pituitary-gonadal (HPG) axis or due to *peripheral* causes, e.g. exogenous administration/endogenous overproduction of gonadal steroids. Peripheral puberty is usually limited to premature development of one or more secondary sexual characteristics, e.g. thelarche or adrenarche, *without* actual reproductive maturation (Ch 22.6.2).

Delayed puberty denotes maturational lag in HPG axis, as indicated by:
- Absence of first pubertal indicator by 13 years in girls (primary breast mound) and 14 years in boys (testicular enlargement),
- A Gap of > 5 years between first sign of puberty and completion of genital growth/menarche, or
- Absence of menarche by 15 years in females.

Delayed puberty is usually *constitutional*, with similar family history and simultaneous delay in height and bone age. *Pathological* delay may be due to central gonadotropin deficiency or peripheral non-responsiveness to these hormones (Ch 22.6.2).

B. Physical problems: Adolescents are susceptible to broad range of physical problems due to growth spurt, increased physical activity, hormonal changes and environmental influences.

Nutritional problems: Common nutritional problems in adolescents include: (a) *iron deficiency* anemia, more likely in girls due to menstrual losses, (b) *calcium deficiency*, due to rapid skeletal growth with less sun exposure, (c) *iodine deficiency* due to increased requirement, i.e. pubertal goiter, (d) undernutrition or obesity due to faulty food habits and changing life style. Adolescents are also prone to psychogenic eating disorders, e.g. anorexia nervosa, discussed later.

Obesity is emerging as a major cause of concern in Indian adolescents due to inappropriate dietary habits and sedentary life style, with immediate risk of developing of low self-esteem due to poor body image and later risk of serious diseases, e.g. diabetes, hypertension, coronary heart disease, strokes and malignancies.

Skin problems, specific during adolescence, usually relate to hormonal changes and imbalance, e.g. *acne* and *hirsutism*. Hirsutism, i.e. androgenic male hair pattern in females, is frequently familial or iatrogenic in origin (steroids, minoxidil, dilantin) and should be distinguished from pathological *virilization*, which is associated with early appearance of secondary sexual characteristics as well.

Orthopedic problems in adolescents originate due to rapid growth of long bones, consequent hypertraction over muscle/tendon insertions and increased sports activity. Important orthopedic problems, specially pertaining to adolescents include—*idiopathic adolescent scoliosis*, *slipped capital femoral epiphysis*, *rheumatoid disorders* and *sports injuries*, etc.

Systemic illnesses: Many physical illnesses, e.g. hypertension, diabetes and rheumatic disorders precipitate or exacerbate during adolescence, due to increased metabolic demands and activity.

TABLE 13.4: Causes of gynecomastia

- Benign gynecomastia in adolescents
- *Drugs:* NSAIDs, digoxin, INH, hormones
- Chronic liver or renal disease
- *Tumors:* Adrenal, gonadal, etc.
- *Endocrinal:* Hypogonadism, hyperthyroidism

At the same time, many childhood illnesses tend to improve, disappear or enter into long remissions at puberty, e.g. asthma, nephrotic syndrome, rheumatic fever, sino-pulmonary infections, etc., due to hormonal changes or reduced risk of environmental exposure.

C. Breast problems: *Physiological variations*, e.g. asymmetric breast size, marginally delayed thelarche or transient nipple discharge in girls and transient gynecomastia in boys are common causes of concern during adolescence, though most of these are normal variations and do not require any intervention except reassurance.

Gynecomastia, i.e. *breast enlargement in boys* is common (~50–60%) during mid-adolescence, which may be unilateral or bilateral and tender or non-tender. Usually, it is a benign process due to hormonal changes that regresses spontaneously within few months and no treatment is required except reassurance. Pharmacotherapy with bromocriptine is indicated only in severe cases with significant physical or psychological discomfort. However, persistent or progressive gynecomastia in adolescents may be pathological **(Table 13.4)** and needs evaluation.

Congenital anomalies, e.g. *amastia* (absent breast), *athelia* (absent nipple), *polymastia* and *polythelia* (supernumerary breasts or nipples), are usually unilateral and frequently missed till adolescence.

Amastia may be associated with *Poland syndrome* (aplasia of pectoralis muscle, rib abnormalities, webbed fingers and radial aplasia). Supernumerary breasts/nipples commonly present along the milk-lines-drawn from shoulder-tip to xiphisternum. Surgical intervention is rarely needed in these cases, except for cosmetic purpose.

Breast hypertrophy or masses may be physiological or pathological **(Table 13.5)**.

Virginal hypertrophy, i.e. massive bilateral breast enlargement in females probably indicates end-organ hypersensitivity to estrogens and may require reduction mammoplasty after late adolescence.

Mastodynia, the painful cyclical breast engorgement, during ovulation/menstruation time is common in late adolescence, which should be treated with analgesics and bra support.

Unilateral breast lumps in adolescence are usually benign, e.g. fibroadenoma (commonest), but rare risk of malignancy must to be excluded by FNAC or biopsy.

TABLE 13.5: Causes of breast masses

- Virginal hypertrophy
- Mastodynia
- Fibroadenoma (commonest mass in adolescence)
- Fibrocystic breast disease
- Mastitis or breast abscess
- *Malignancy:* Rhabdomyosarcoma, lymphoma
- Gynecomastia in boys due to any cause **(Table 13.4)**

TABLE 13.6: Causes of nipple discharge

- *Benign:* Local stimulation
- Pregnancy
- *Drugs:* Contraceptives, methyldopa
- ↑ *prolactin:* Pituitary adenoma, hypothyroidism#
- *Local*:* Ductal ectasia, papilloma, malignancy

* blood-tinged discharge # due to ↑ TRH

Nipple discharge: Transient milky or sticky nipple discharge in adolescent girls is not uncommon due to physical stimulation *or* drugs, e.g. contraceptives. However, persistent *galactorrhea* or blood-tinged discharge needs to be investigated for pathological causes **(Table 13.6)**.

D. Menstrual problems: Mean age of menarche in Indian girls is ~12.5 years (10–16 years) and initial cycles for first 12–18 months are often irregular and anovulatory. Menstrual onset, frequency and duration pattern usually correlates well with maternal pattern

Amenorrhea may be *primary*, i.e. absent menstruation till 16 years of age, despite breast development or *secondary*, i.e. cessation of menstruation for >3 months, after previous regular periods; due to various causes **(Table 13.7)**. Teenage pregnancy is increasingly common and needs to be excluded in cases of secondary amenorrhea.

Dysmenorrhea, i.e. lower abdominal pain or cramps during menstruation occurs in ~60% of teen-girls, frequently leading to school absenteeism. Most cases

TABLE 13.7: Causes of amenorrhea

Primary amenorrhea

- Physiological delay
- Undernutrition
- *Hypothalamic:* GnRH deficiency
- Hypopituitarism
- Gonadal dysgnenesis, e.g. Turner syndrome
- Utero-vaginal anomalies, e.g. imperforate hymen
- *Others:* Hypothyroidism, cortisol excess, etc.

Secondary amenorrhea

- Pregnancy
- *Transient:* Dieting, heavy exercise, stress
- Chronic medical illnesses
- *Endocrinal:* Hypopituitarism, hypothyroidism
- *Gonadal:* Polycystic ovary, pelvic radiation/surgery
- Utero-vaginal synechiae
- *Drugs:* Oral contraceptives, phenothiazines

TABLE 13.8: Causes of abnormal uterine bleeding

- Dysfunctional uterine bleeding (DUB)
- Threatened abortion/ectopic pregnancy
- Vaginal infections, trauma or foreign body
- *Uterine:* Endometriosis, congenital anomalies
- *Ovarian:* Polycystic ovary, tumors
- Pelvic inflammatory disease
- Systemic bleeding disorders
- *Endocrinal:* Thyroid or adrenal disorders
- *Drugs:* Oral contraceptives, aspirin

may be treated with rest and anti-inflammatory agents. Severe or secondary dysmenorrhea after initial painless cycles must be investigated for—(a) pelvic inflammatory disease, (b) endometriosis, (c) intrauterine devices, (d) utero-vaginal anomalies/tumors, and (e) ectopic pregnancy.

Abnormal uterine bleeding may be *dysfunctional* (no underlying pathology) or *secondary* **(Table 13.8)**.

Dysfunctional uterine bleeding (DUB) is a diagnosis of exclusion, usually associated with anovulatory cycles without progesterone production and unopposed estrogen excess. Treatment of severe DUB includes cyclic estrogen-progesterone therapy and iron supplementation.

E. Urogenital problems: Urogenital problems are common in adolescence due to increasing genital concerns, local mucosal susceptibility due to hormonal changes and precocious sexual activity.

Physiological leucorrhoea, i.e. thin, mucoid, acidic and non-foul smelling discharge, usually before menstruation, is common in adolescent girls due to high estrogen levels and needs no treatment except reassurance. However, any purulent, bloody or foul smelling discharge or that associated with pruritis or urinary complaints needs evaluation **(Table 13.9)**.

Non-specific vaginosis (NSV) is the commonest cause of pathological vaginal discharge in adolescent girls, due to: (a) inadequate external protection due to lack of labial pad of fat and pubic hair, (b) thin, atrophic, less acidic vaginal epithelium, (c) close proximity with anal orifice, and (d) experimental sexual activity, e.g. masturbation.

TABLE 13.9: Causes of vaginal discharge

- Physiological leucorrhoea
- Non-specific vulvovaginitis
- Vulvo-vaginal candidiasis
- Sexually transmitted diseases
- Genital trauma or foreign body
- Urethral prolapse
- Genital tumors

Common microbial etiology of NSV includes fecal pathogens, e.g. enterococci, *Staph. aureus*, anaerobic pathogens, candida, etc.

Management of these cases include: (a) good perineal hygiene, (b) symptomatic treatment, (c) topical antifungal/antibiotic agents, and (d) systemic antibiotics in selected cases. NSV need to be differentiated from more serious STDs with vaginal discharge.

Superficial perineal infections, e.g. intertrigo, fungal infections or pediculosis, etc. are common **in** both sexes due to poor perineal hygiene, use of tight underwears and sweat-induced moisture. Presence of fungal infection may be confirmed with wet KOH preparation and treated with topical antifungals, e.g. clotrimazole.

Sexually transmitted diseases (STDs) are often underdiagnosed in adolescence and may be acquired by casual contact or genital handling with contaminated fingers. According to the syndromic approach, clinical presentation of STDs may be broadly divided into *four* groups—*(a) vaginal or urethral discharge, (b) ulcerative genital lesion, (c) inguinal lymphadenopathy, and (d) pelvic inflammatory disease (PID).*

Although detailed discussion of STDs is beyond the scope of this book, a short summary of common STDs is presented in **Table 13.10**.

Congenital urogenital tract anomalies, though present since birth, are frequently noticed first time during adolescence due to menstrual problems (imperforate hymen, vaginal septa/atresia and uterine anomalies) and increased genital concerns (epispadias, hypospadias or undescended testes).

TABLE 13.10: Common sexually transmitted diseases in adolescents

	Pathogen	*Clinical feature*	*Diagnosis*	*Management**
Gonorrhea	*N. gonorrhoeae*	Discharge/PID	Gram stain	Cefixime
Chlamydia	*C. trachomatis*	Discharge/PID	Serology	Azithromycin
Trichomonas	*T. vaginitis*	Discharge	Microscopy	Metronidazole
Syphilis	*T. pallidum*	Painless ulcer	Serology	Benzathine Penicillin
Chancroid	*H. ducreyi*	Painful ulcer	Microscopy	Erythromycin
Genital herpes	*H. simplex II*	Multiple vesicles	Microscopy	Acyclovir
Genital warts	HPV	Painless warts	Clinical	Cryotherapy

*in uncomplicated disease, **PID:** Pelvic inflammatory disease

13.3 PSYCHOSOCIAL PROBLEMS IN ADOLESCENCE

Adolescents are highly susceptible to behavioral problems due to emotional turmoil and search for the independence, sometimes crossing the social barriers with substantial anti-social dimensions

Prevalence of mental health problems in Indian adolescents is estimated to be about 10–15%, though many of them remain unrecognized due to ignorance and taboo attached to them. Common psychological problems in this age group may be broadly divided into following categories:

- *Adaptive disorders,* e.g. depression, suicide, juvenile delinquency, etc.
- *Psychosomatic disorders*, e.g. anorexia nervosa, bulimia, conversion reactions, etc.
- *Disorders of sexuality*, e.g. masturbation, pregnancy.

Some common mental health issues in adolescents are discussed as follows:

Anorexia nervosa (AN) is an increasing common behavioral problem in adolescent girls, characterized by:

- Intense fear of obesity despite weight loss,
- Denial of weight loss, even if obvious,
- Refusal to maintain weight above minimal limits,
- Secondary amenorrhea for >3 cycles in females.

Epidemiology: AN is estimated to be prevalent in ~1–5% of teen girls, with a female to male ratio of 20:1. Important *risk* factors for AN include-family history, low-self esteem and preoccupation with self-image.

Clinical manifestations usually begin in adolescence with moderate efforts of dieting to improve the self-appearance, which ultimately progress to severe malnutrition. Two type of dieting efforts prevail-*restricted-eating* and *bulimic-type*, i.e. binge-eating with self-induced vomiting. Gradually the patient becomes extremely cachexic with rough and scaly skin, alopecia, constipation and signs of vitamin/mineral deficiency.

More severe cases may also develop complications, e.g. (a) dehydration/dyselectrolytemia, (b) postural hypotension, (c) neuropsychological problems, (d) pancytopenia, and (e) endocrinal problems, e.g. amenorrhea. About 10% of them may even die due to severe dehydration/shock, dyselectrolytemia and anemia.

Management of AN requires a combination of nutritional rehabilitation and psychotherapy, e.g. behavioral modification. Pharmacotherapy with antidepressants are useful only in cases with associated depression.

Bulimia nervosa (BN) is a distinct entity from AN, characterized by recurrent episodes of:

- Binge-eating, e.g. compulsive excessive and frequent eating, followed by;
- Inappropriate efforts to control weight gain, e.g. self-induced vomiting or misuse of laxatives, diuretics, enema, etc.

Unlike AN that is common in girls with low self-esteem, BN is more common in girls with impulsive or anti-social personalities like those with history of drug abuse, sexual promiscuity and suicidal attempts and stealing. Electrolyte abnormalities due to excessive vomiting or laxative use is the predominant morbidity in these cases.

Management includes a combination of nutritional monitoring, psychological support and antidepressants.

Substance abuse: Although experimental substance abuse may be considered as part of normal psychosocial development, habitual or compulsive abuse among adolescents has shown a distinctly upward trend during recent years.

Commonly used substances in India are alcohol, nicotine and volatile substances, e.g. spirit and shoe polish. Drug abuse due to other agents, e.g. hallucinogens (LSD or *ecstasy*), barbiturates, opiates and cocaine is rising; as also the use of anabolic steroids to enhance atheletic performance.

Risk factors for substance abuse include—(a) social and peer pressure, (b) emotional stress, (c) low-self-esteem, (d) family maladjustments, and (e) lack of inhibitory influences. Role of unknown genetic or biological factors has been postulated in cases with severe substance abuse or dependence.

Clinically, substance abuse should always be suspected in any adolescent with unexplained: (a) abnormal behavior, e.g. depression or mood elevation, (b) physical signs, e.g. respiratory depression, coma, papillary abnormalities, and (c) superficial indicators, e.g. unexplained needle marks or breath odor.

Management of these cases includes: (a) treatment of acute episodes with specific antidotes and supportive measures, (b) enrolment in long-term detoxification programs, (c) psychological evaluation and counseling of patient and family, (d) elimination of precipitating factors, and (e) rehabilitation in the school, family or workplace.

Masturbation, i.e. stimulation of one's own genitals to derive pleasure, is not an uncommon behavior even in pre-adolescents but becomes more common in adolescence with an incidence of as high as 90% in boys and 30% in girls. It may also be a manifestation of sexual abuse or exposure to explicit sexual material/events.

However, compulsive, intense masturbation that disturbs other activities, inter-personal relationships or involves use of objects/public display is not normative and needs counseling. Parents must be counselled about normal nature of this act. Moral lectures or punishment only intensifies this behavior. Behavioral therapy is

indicated only in rare selected cases with compulsive acts, leading to development of guilt and anxiety in adolescents and their parents.

Teen pregnancy is estimated to account for ~15% of all pregnancies in India and often get underreported.

Epidemiologically, three important risk factors for teen pregnancy in India are—(a) early marriage as a prevalent social custom in many backward regions, (b) experimental tendencies in adolescents (unwed mothers), and (c) inadequate sexual education or awareness about contraceptive methods.

Consequences of teen pregnancy are disastrous not only to mother but also to family and offspring **(Table 13.11)**. Maternal and infant mortality rates in teen mothers are ~2–3 times higher than in general population.

Prevention: Although legal barriers for early/childhood marriages are already in place in India, important preventive measures against teen-pregnancies include-(a) social reforms and community-awareness campaigns to discourage child marriages, (b) adolescent counseling at every contact level, regarding hazards and protection methods, (c) changes in adolescent-parent communication ties, (d) promotion of female literacy, and (e) easy and confidential availability of birth control education, devices and obstetrical care.

Teen-suicide: Suicide is the third leading cause of adolescent mortality in India and the fifth leading cause, globally.

Adolescents are at risk for suicide or attempted suicide due to cognitive immaturity and impulsivity. Successful attempts are more common in boys while failed attempts are more common in girls.

Adjustment disorders, anxiety and depression, substance abuse, physical/sexual abuse and parent-child conflict are common causes of suicide in adolescents.

Family history of suicide and non-suicidal self-injury behavior, i.e. deliberate destruction or alteration of body tissue without suicidal intent to cope with mental distress or secure attention are important risk factors for suicide in teens.

Many scoring systems have been developed to assess the risk of self-inflicted injury or suicides in teens, which can be used to identify high-risk cases and refer them for mental health support. HEEADSSS screening, a useful tool to assess psychosocial history in adolescents may also be used to identify high-risk cases (Ch 13.4).

TABLE 13.11: Consequences of teen-pregnancy

Maternal *(high maternal mortality)*
- *General:* Undernutrition, anemia, osteoporosis
- *Local:* Vaginal infections and STDs
- *Psychological:* Distress, depression and suicides

Obstetrical
- Cephalopelvic disproportion
- Peurperal sepsis
- Birth-canal trauma

Neonatal *(high perinatal/infant mortality)*
- Abortions and stillbirths
- Prematurity and low birth weight
- Neonatal sepsis

Socioeconomic
- Social ostracization
- Economic drawbacks
- Increased cost of health care

13.4 ADOLESCENT HEALTH CHECK-UP

Assessment of an adolescent in terms of medical issues must follow the same process as for others, though some issues are important and needs to be considered:

- **Privacy and confidentiality:** Most adolescents prefer to discuss their health issues or concerns on one-to-one basis and may be hesitant to open-up even in presence of parents or friends. Due regard for privacy is necessary during health assessment of an adolescent to permit him to discuss his/her concerns in a frank and friendly manner, without any disturbance or inhibition.

  Confidentiality is an assurance between adolescent and health-provider not to share the information exchanged between them during the assessment process, unless contravening the law or exposing him/her to harm, e.g. suicide, abuse, etc.
- **Communication and rapport building:** Health-care provider must be empathetic and non-judgement towards the adolescent to ensure good communication. Use of simple ice-breaker questions before sensitive questions, showing interest in their concerns and permitting them to express freely without arguments will allow building of a rapport between HCW and adolescent.
- **History-taking:** History must be first obtained by the adolescent himself/herself before inving the parent to collaborate, if required. It is also advisable to go beyond the presenting complaints and enquire about other issues as well as family/school environment.

  HEEADSSS is an acronym of a very useful tool to assess psychosocial history in almost all domains in adolescents. It includes eight components representing assessment of **H**ome environment**, E**ducation/employment status, performance and expectations, **E**ating/Exercise behavior including recent changes, **A**ctivities, hobbies and peer-relationships, **D**rug abuse/experimentation, **S**exual activity/behavior, **S**uicide and mood/mental health status and **S**afety/spirituality behavior including risk-taking.
- **Consent** is necessary from all adolescents 18 years of age for any examination/procedure, irrespective of the parental consent or refusal to consent and must be recorded in writing after due explanation.

In adolescents 12–18 years of age, both, an assent from them and a consent from parent is required. Parental consent is enough for children <12 years, though they must be explained the need and process of examination/procedure irrespective of the age.

- **Physical examination** must include assessment of physical growth by anthropometry vis a vis reference norms, sexual maturity using Tanner's SMR staging and detailed general and systemic examination. However, adolescents are often quite sensitive and vulnerable and following precautions are must during physical examination:
  - Record the consent before examination, as discussed earlier.
  - Ensure that a chaperone (Nurse/relative) of same sex as adolescent is present, if gender of the doctor differs from the patient.
  - Ensure complete privacy in the examination room by closing the door or using heavy curtains
  - Explain the adolescent steps and scope of examination, including the need for it, specially when assessing SMR.
  - Watch for any discomfort or change in the behavior of adolescent and abort the examination if required.
- **Disclosure:** Explain the assessment findings at the end as well as interpretation and the need for further assessment, referral, follow-up or investigations.
- **Information, education and counseling:** All opportunities to interact with adolescents should be used to provide them necessary information about nutrition, sexual changes, life-style and mental health issues, other than addressing their specific health concerns.

  Anticipatory guidance is defined as proactive counseling about expected physical, motional, psychological, and developmental changes in adolescents till next health visit to prepares them and their families for what to expect next in their child's development.
- **Referral**, if necessary for speciality services or other service delivery points, e.g. integrated counseling testing centre, de-addiction centres, social workers, mental health professionals, etc., after explaining the need for such referral.

Under the *Protection of Child Rights Act, 2005* and *Protection of Child from Sexual Offenses Act (POCSO) 2012*, it is mandatory to inform regulatory authorities, if a heath care worker comes across any suspicion act of physical or sexual abuse during the assessment process in a child or adolescent < 18 years of age.

13.5 ADOLESCENT FRIENDLY HEALTH SERVICES (AFHS)

Adolescents, generally considered as healthy, are actually at higher risk for many nutritional, life-style, sexual and mental health as well as violence and injuries. Unfortunately, existing health facilities are neither adequate nor appropriate to provide adolescent-friendly services, who are also hesitant to utilize them due to concerns, e.g. privacy, confidentiality, judgmental attitudes of staff as well as myths, misconceptions and lack of awareness.

Concept of Adolescent Friendly Health Services (AFHS) was first coined by WHO (2000), to provide broad range of preventive, promotive and curative services, specially dedicated to this age group under one roof to improve availability, accessibility and utilization.

India adopted a two-pronged strategy to provide adolescent-specific services at public health facilities during routine hours as well as n dedicated days/times since 2006 as *Adolescent Reproductive Sexual Health* (ARSH) Clinics, later expanded as AFHS clinics under *Rashtriya Kishor Swasthya Karyakram* (RKSK).

These services are delivered through trained service providers including health staff and counsellors at existing health centers, out-reach centers, e.g. schools/colleges or through telemedicine or social media. Now, many governmental, private and voluntary health agencies run dedicated AFHCs, sometimes with different names, e.g. youth clinics, youth friendly center, Jagruti, Jigyasa, etc.

Objectives: AFHCs aims to provide whole gamut of clinical and counseling services on diverse adolescent health issues including: (a) sexual and reproductive health, (b) nutrition, (c) substance abuse, (d) injuries and violence, (e) non-communicable diseases, and (f) mental health.

Functions: AFHCs aim to provide following services:

- ***Promotion of healthy life-style*** by appropriate counseling regarding nutrition, sleep and avoidance of substance abuse.
- ***Information, education and communication/counseling (IEC)*** for reproductive/sexual health issues, health concerns and life-style diseases as well as the availability of support system.
- ***Preventive services,*** e.g. growth assessment, immunization and identification of risky behavior for life-style diseases, mental health problems or social adjustment issues.
- ***Establishing a rapport*** to provide them a channel to discuss their concerns, including setting up of 24-hour help-lines.
- ***Curative services*** to diagnosis and management of health problems issues including age-specific problems,
- **Referral** to appropriate health facilities or other service delivery points, e.g. Integrated Counselling Testing Centre (for HIV), de-addiction centres, etc.

- ***Sensitize the caregivers and influencers*** on various adolescent health issues and apprise them of various available adolescent friendly health services.

Attributes: The concept "***Friendly***" in AFHCs denotes that these services should be *accessible, equitable, acceptable, appropriate, comprehensive and efficient.* These clinics should also have further referral linkages with the higher facilities and specialty clinics.

AFHC staff is specially trained to: (a) show respect for adolescents with a non-critical approach towards issues, specially related to reproductive/sexual health, (b) ensure privacy and confidentiality without sharing information provided by them with others, including parents, (c) spend adequate time and have patience to make the adolescent feel comfortable to discuss all issues related to puberty such as body image, relationships and sexuality.

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CHAPTER

14

Gastrointestinal Disorders

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Gastrointestinal tract (GIT) disorders are the second commonest cause of morbidity and mortality in Indian children, after respiratory disorders.

14.1 BASIC CONSIDERATIONS

Embryologically, GIT is largely derived from primitive *endodermal* gut tube **(Fig. 14.1)**, except the oral cavity and anus, which develop from ectodermal invaginations on two ends of this tube. In early fetal life, two membranes-buccopharyngeal and cloacal membranes, separate primitive gut tube from oral cavity and anus, respectively.

During 4–5th week, this tube elongates and divides into three segments—foregut, midgut and hindgut. The *primitive foregut* develops into pharynx, esophagus, stomach and proximal duodenum, while ancillary structures, e.g. liver, gallbladder and pancreas are derived from its ventral and dorsal outpouches, distal to the stomach. Another ventral outpouching of gut, proximal to primitive stomach, develops into respiratory tract and lungs.

The *primitive midgut* is connected to the yolk sac via *vitelline or omphalomesentric* duct till 6–8 weeks, though its proximal part may remain patent in 1–2% population as *Meckel's diverticulum*. Distal half of duodenum, small intestine, ascending colon and right 2/3rd of transverse colon develop from midgut.

The *primitive hindgut* develops into left 1/3rd of transverse colon, descending colon and rectum till the cloacal membrane, to join ectodermal anus. Lower part of this hindgut is vertically divided into two parts-anterior urogenital sinus to form urogenital system and posterior cloacal sinus to form upper part of anal canal. *Vascular and muscular layers* of gut are derived from mesoderm, while neural elements migrate from the neural crest to differentiate into intrinsic autonomic plexus. GIT also receives extrinsic nerve supply form vagus and splanchnic nerves.

Anatomically, Basic architecture of all parts of GIT is similar, composed of four layers from in-outwards—(a) *mucosal layer* with its three parts—epithelium, lamina propria and muscularis mucosae, (b) *submucosal layer*, (c) *muscularis propria* with inner circular and outer longitudinal smooth muscles and intervening myenteric plexus, and (d) *serosal or adventitious layer*. However, variations in mucosal and muscular structure as well as presence of exocrine glands and enzymes, determine specific functions of each part.

Physiologically, apart from the primary function of food assimilation, GIT also acts as physical and *immunological*

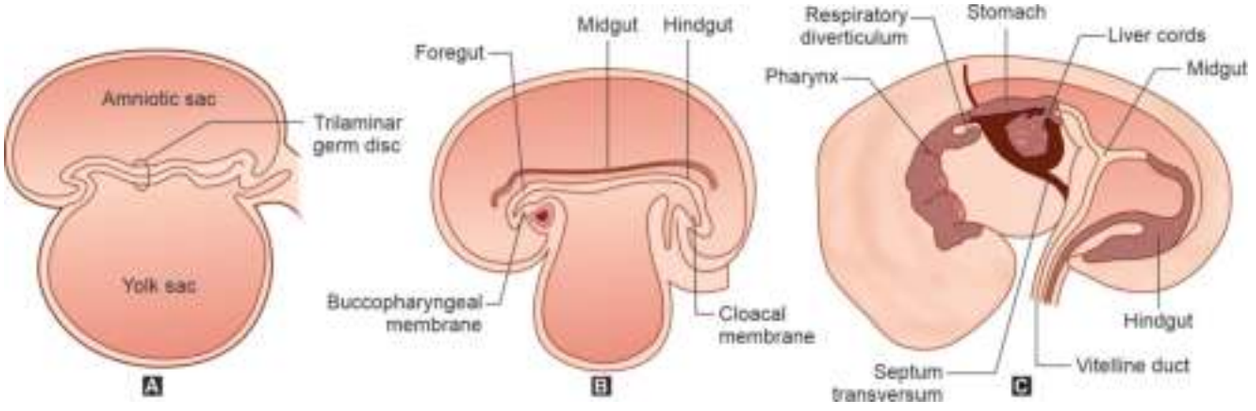

Fig. 14.1: **Development of gastrointestinal tract.**

barrier between external and internal environment, as well as an *endocrinal organ* to produce various hormones.

PHYSIOLOGY OF DIGESTION

Digestion and absorption of nutrients is a complex process, involving various digestive enzymes and transporter mechanisms, as follows:

- **Carbohydrates,** which contribute to ~60–70% of diet, are consumed as polysaccharides (starch, dextrin), disaccharides (sucrose, maltose, lactose) or monosaccharides (glucose, fructose and galactose).

  Digestion of carbohydrates involves conversion of all polysaccharides and disaccharides into monosaccharides by salivary and pancreatic amylase, and then by intestinal disaccharidase enzymes, e.g. lactase, sucrase, maltase, isomaltase, etc. Lactose splits into glucose and galactose, sucrose into glucose and fructose and maltose into two molecules of glucose. Disaccharidase enzymes are mainly present on brush borders and easily lost in diarrhea or severe malnutrition to cause carbohydrate intolerance.

  Absorption of monosaccharides across the intestinal mucosa is an active, energy-consuming process involving specific carrier substances. Glucose, sodium and certain amino acids share some of these carrier substances (basis for oral rehydration therapy).
- **Proteins,** constituting ~15–20% of diet, are consumed as complex organic compounds, which need to be split into smaller peptides or constituent amino acids before absorption. However in newborns, even intact protein molecules may be transported across the mucosal cells via *pinocytosis,* leading to sensitization of immune cells in lamina propria (basis for atopic disorders after early top-feeding).

  Digestion of complex proteins into smaller peptides/amino acids requires many enzymes, including (a) *pepsin* from pyloric and duodenal glands, (b) *trypsin* from pancreas, (c) *enterokinase* from brush borders and (d) *peptidase enzymes* in intestinal mucosal cells. In addition, gastric acid denatures proteins for easier digestion as well as activates Pepsinogen to Pepsin.

  Absorption of amino acids is also an active process, requiring many transport systems. Many amino acids share common transport mechanism, and compete with each other for absorption (basis for Pellagra in *maize-eaters*, in whom high leucine content of maize interferes with absorption of tryptophan-a niacin precursor).
- **Fats,** which form ~15–20% of diet, are consumed as visible fats (ghee, oils) or invisible fats (cereals, pulses). Biochemically, fats may be classified as *simple fats*, e.g. triglycerides (most abundant, ~98%), *derived lipids*, e.g. cholesterol and *compound lipids*, e.g. phospholipids.

  Digestion of fats requires hydrolysis of triglycerides by pancreatic *lipase* to convert into diglycerides, then monoglycerides and ultimately, into fatty acids and glycerol. *Bile salts* from the liver activate lipase and emulsify fats to convert fat-soluble monoglycerides and fatty acids into water-soluble *micelles*. *Lipase,* which is also present in salivary and gastric secretion, contributes in pre-pyloric partial fat digestion.

  Absorption of fats is a complex process. When micelles come in contact of intestinal epithelium, monoglycerides and fatty acids diffuse into mucosal cells and remaining part of the micelle, i.e. bile acids, move back into lumen for re-utilization. Inside the mucosal cell, monoglycerides are further hydrolyzed by intracellular *lipase* into fatty acids and glycerol. While water-soluble glycerol quickly enters into portal circulation, long-chain fatty acids are re-esterified into triglycerides. These triglycerides, along with cholesterol and phospholipids form a globular mass, i.e. *chylomicrons* which are extruded into the intercellular space to pass through lacteals to thoracic duct and finally reach to circulation.

Unlike long-chain fatty acids, medium-chain fatty acids do not require re-esterification and absorbed directly into the portal circulation (basis for the use of medium chain triglycerides as predominant fat in liver diseases).

Physiology of digestion and absorption for micronutrients has been discussed in respective chapters.

14.2 CLINICAL EVALUATION OF GIT DISEASE

Evaluation of GIT disease depends on presenting symptoms though general aspects are as follows:

I. History in GIT disease should include *onset*, *duration* and *progression* of presenting complaints, apart from review of general GIT functions, e.g. dietary intake, feeding habits and appetite as well as frequency and nature of stools,. Past history of worm infestations or recent travel and environmental history regarding water supply and sanitation should also be recorded.

II. General examination specially relates to anthropometric parameters, local examination of oral cavity and signs of dehydration, micronutrient deficiencies or hepatic dysfunction. Search for extra-intestinal septic focus as well as cardiovascular and respiratory examination is equally important to assess the cause/effect of GIT disorders.

III. Abdominal examination is the most important and specific component of GIT evaluation, which includes: *inspection, palpation, percussion* and *auscultation* of abdomen as well as *examination for genitals, hernia sites and spine.*

- **Inspection** involves visual examination for—(a) abdominal shape and appearance of skin, (b) movements

with respiration, (c) umbilical site, (d) superficial abnormalities, e.g. scars, sinuses and dilated veins, (e) hernia sites, (f) genitals, and (g) perineum.

Abnormal shapes include scaphoid (diaphragmatic hernia) or distended abdomen. Asymmetrical abdomen may be either due to phantom hernia or underlying mass.

Restriction of abdominal movements during breathing indicates peritonitis, while visible peristalsis may be due to underlying dynamic intestinal obstruction. Paradoxical abdominal movements suggest diaphragmatic paralysis.

Umbilicus is transversely stretched (*smiling umbilicus)* in abdominal distension. Cherry-red swelling of umbilicus in para-neonates indicates umbilical granuloma, while bluish periumbilical pigmentation suggests intra-peritoneal bleeding (*Cullen sign).*

Abdominal veins are normally visible in early infancy or in thin, fair-complexion children. Dilated veins indicate portal hypertension or inferior vena cava (IVC) obstruction, further differentiated by their location and direction of blood flow on *milking-refilling method*—(a) dilated flank and back veins with upward flow indicate IVC obstruction, e.g. Budd-Chiari syndrome, while (b) dilated and radiating periumbilical veins, flowing away from umbilicus (*Caput medusae*) indicate portal hypertension.

Genitals should be examined for descent of testes and urethral opening in males vaginal discharge in females and abnormal fecal passage for anorectal malformations. Inguinal hernia must be specially looked for, in cases of undescended testis.

Perineal inspection for anal patency, fissures or excoriation is essential in all, though per-rectal examination should be avoided and advised only in select cases, e.g. suspected Hirschsprung disease.

- **Palpation** should be done in supine position with semi-*flexed* lower limbs, to confirm inspection findings and assess for: (a) abdominal tenderness, guarding or rigidity, and (b) organomegaly.

  Abdominal tenderness, voluntary guarding or involuntary rigidity may be local or generalized and suggests underlying peritoneal or visceral inflammation. Persistent generalized abdominal rigidity also indicates muscle spasms, e.g. in tetanus. Abdominal girth should always be recorded in cases with distended abdomen, for monitoring.

  Liver must be palpated from right iliac fossa upwards, to record its—(i) size, (ii) span, (iii) surface, (iv) margins, (v) consistency, (vi) tenderness and (vii) pulsations (Ch 15.2). Liver is normally palpable till two years of age.

  Spleen is palpated from right iliac fossa by moving obliquely towards left costal margin. It may be normally palpable in first 3 months. Enlarged spleen must be assessed for size and need to be differentiated from renal mass (Ch 19.16).

  Kidneys are palpated bimanually in supine and standing position. Lower pole of the left kidney may be normally palpable in infants.
- **Percussion** mainly aims to detect presence of fluid in peritoneum by—(a) *fluid thrill* for large ascites, (b) Horse-shoe dullness for moderate ascites, (c) *shifting dullness* for mild fluid collection, and (d) *Puddle sign* in knee-chest position for minimal fluid collection of <50 ml. Percussion is also used to determine liver span and bladder fullness.
- **Auscultation** includes search for abnormal peristaltic activity, renal arterial bruit in renal artery stenosis and periumbilical venous hum suggestive of portal hypertension. Intestinal peristalsis are best heard in left lumbar region with a rate of ~1–3/minute; increased in intestinal obstruction and decreased in paralytic ileus or peritonitis.

14.3 LABORATORY EVALUATION OF GIT DISEASE

Laboratory evaluation in GIT disorders depend on the suspected etiology, though some important investigations are as follows:

I. Stool examination is the baseline investigation for suspected GIT disease. A freshly collected sample should be examined for:

- **Gross characteristics,** which vary according to the age and dietary pattern. Older children on home diet usually pass well-formed stools, which are brownish due to bile pigment and slightly foul smelling due to presence of indole and *skatole* – degradation products of organic matter.

  Gross stool examination includes evaluation of its: (a) bulk, (b) consistency, (c) color, (d) odor, and (e) presence of unusual substances, e.g. blood, mucus or worms.

  Some important diagnostic clues are as follows:
  - Clay-colored stools indicate obstructive jaundice, while black-tarry stools may be due to melena or after iron administration.
  - Rice-water stools indicate cholera or ETEC diarrhea.
  - Hard stools with pellet or ribbon-like appearance indicate Hirschsprung disease.
  - Bulky, pale, extremely foul-smelling stools with fat-globules indicate fat malabsorption (*steatorrhea*).
  - Frothy, explosive and watery stools indicate lactose intolerance.
  - Presence of blood indicates dysentery or GIT bleeding.
- **Biochemical examination** commonly includes: (a) *pH* estimation, (b) Benedict test and (c) Benzidine test.

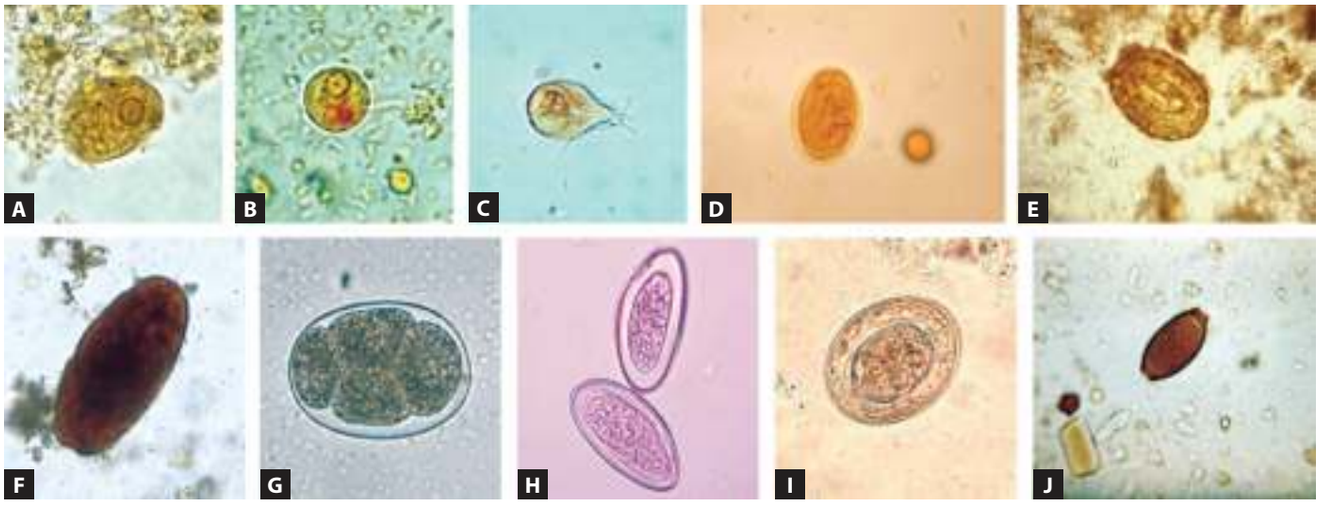

Fig. 14.2: Common ova and cysts on stool microscopy.
(A) *E. histolytica* (trophozoites); (B) *E. histolytica* (cysts); (C) *G. lamblia* (trophozoites); (D) *G. lamblia* (cysts); (E) *Ascaris lumbricoidis* (fertilized egg); (F) *Ascaris lumbricoidis* (unfertilized egg); (G) *Ankylostoma duodenale* (egg); (H) *Enterobius vermicularis* (egg); (I) *H. nana* (egg); (J) *T. trichuria* (egg).

  - Normal stool pH is alkaline, estimated by dipping a pH paper in stool suspension (red turns blue). Acidic stools (blue turns red) indicate lactose intolerance.
  - *Benedict test* detects presence of reducing sugar in stools, e.g. in disaccharide intolerance, performed in similar manner as for urine, except the use of a stool-saline suspension instead of urine sample (Ch 21.2).
  - *Benzidine test* detects presence of occult blood in stools, e.g. in hookworm infestations, performed in similar manner as for urine, except the use of a stool-saline suspension (Ch 21.2).
- **Microscopic examination:** An unstained slide of saline stool suspension should be examined for-(a) cellular elements, e.g. RBCs or pus cells, (b) ova/cysts of protozoa and parasites **(Fig. 14.2)**. Iodine staining for nuclear structures is commonly used to differentiate organic from inorganic matter.

  Hanging-drop preparation is essential in rice-water diarrhoea to exclude cholera. A drop of fresh stool sample is placed on cover-slip, which is then inverted on a slide to *see darting motility* of *V. cholerae* on microscopy.

II. Radioimaging studies: The choice of radioimaging depends on the suspected etiology, though common methods include:

- **Plain X-rays** are of limited use in GIT evaluation due to presence of gases and limited air-tissue contrast. However, an erect X-ray is essential in *acute abdomen* and must be evaluated for: (a) multiple air-fluid levels* in intestinal obstruction, (b) gas under diaphragm in intestinal perforation, extra-abdominal soft tissue, (c) lower lung abnormalities in basal pneumonitis/pleuritis, (d) foreign bodies and other obvious lesions, e.g. musculoskeletal deformities.

  *Up to three air-fluid levels are normal in standing X-ray abdomen, denoting interface at stomach, ileocaecal region and sigmoid colon. More than >3 levels indicates paralytic ileus or mechanical intestinal obstruction.
- **Barium studies** are more useful to delineate structural abnormalities and include: (a) *barium swallow* for suspected esophageal pathology, (b) *barium meal* for suspected gastric pathology, (c) *barium meal with follow-through* for small intestinal lesions, and (d) *barium enema* for colonic lesions.
- **Ultrasonography** is the preferred base-line investigation for evaluation of almost all abdominal pathologies including visceral masses, ascites and even unexplained presentations. CT/MRI is indicated only in selected cases to supplement USG findings.

III. Endoscopy is being increasing used for various diagnostic and therapeutic procedures in children with suspected GIT disorders **(Table 14.1)**. While *upper GI endoscopy* provides an opportunity to visualize from esophagus till duodenum and proximal jejunum, *colonoscopy* is used to reach pathologies from anal canal till distal ileum through ileocaecal valve.

14.4 COMMON PRESENTATIONS IN GIT DISEASE

Clinical manifestations in GIT disorders depend on the site of pathology. While *upper GIT lesions* usually present with dysphagia, vomiting, epigastric/retrosternal pain or hematemesis; *lower gut disorders* manifest with diarrhea, abdominal pain, distension, mass, constipation or hematochazia. However, such distinction is usually

TABLE 14.1: Common indications for GIT endoscopy

Diagnostic visualization
- Unexplained dysphagia
- Unexplained hematemesis
- Suspected foreign body
- Suspected GER, esophageal varices, gastric ulcers
- Chronic diarrhea or malabsorption syndrome

Diagnostic procedures
- GIT biopsy
- Collection of GIT secretions
- ERCP studies*

Therapeutic interventions
- Sclerotherapy
- Foreign body removal
- Dilatation of anorectal malformations
- Colonic surgery, e.g. polyp removal

GER: Gastroesophageal reflux; **ERCP:** Endoscopic retrograde cholangio-pancreatography.

TABLE 14.2: Causes of dysphagia

- **Oropharyngeal lesions**
  - *Congenital:* Cleft-palate, macroglossia
  - *Inflammatory:* Stomatitis, tonsilopharyngitis, diphtheria
  - *Extrinsic:* Retropharyngeal abscess, tumors
- **Esophageal lesions**
  - Strictures—congenital, GER, corrosive poisoning
  - Foreign body
  - *Inflammatory:* Reflux esophagitis, candidiasis*
  - *Extrinsic:* Aortic ring, mediastinal tumors
- **Neuromuscular un-coordination**
  - Physiological in preterms
  - Bulbar/pseudobulbar palsy (transfer dysphagia)
  - Achalasia/Hiatus hernia
  - *Motility disorders:* Riley-Day syndrome, myasthenia

*important in immunocompromised host.

obscured in later stages and hence, the onset, duration and progression of complaints are highly informative in clinical diagnosis. This chapter deals with common clinical presentations of GIT disorders, excluding diarrhea discussed later in Ch 14.10.

14.4.1 DYSPHAGIA

Swallowing is a voluntary as well as reflex activity, initiated by the presence of food or saliva in oral cavity and requires close coordination between—(a) closure of nasopharynx by soft palate to prevent nasal regurgitation, (b) closure of glottis to prevent aspiration and (c) relaxation of upper esopharyngeal sphincter to transfer food bolus into esophagus. Further esophageal passage is facilitated by peristaltic waves, culminating into relaxation of lower esophageal sphincter and transfer of food into stomach.

Dysphagia, i.e. difficulty during deglutition indicates either obstruction in food passage *(Mechanical dysphagia) or* neuromuscular incoordination in swallowing mechanisms *(Transfer dysphagia).*

Etiology: Foreign body ingestion is the commonest cause of acute dysphagia in childhood, while chronic dysphagia may be due to impacted foreign bodies or bulbar/pseudobulbar palsy **(Table 14.2)**.

Diagnostic evaluation in dysphagia includes:
- ***Detailed history,*** specially for foreign body ingestion, and relationship of dysphagia with type of foods. Neuromuscular dysphagia is more marked with ingestion of liquids, while difficulty in swallowing solids indicates mechanical obstruction.
- ***Throat examination*** to exclude local pathology, and detailed ***neurological evaluation*** for neuromuscular disorders.
- ***Relevant investigations,*** e.g. (a) X-rays for foreign body, (b) barium swallow for strictures, foreign body and achalasia, (c) esophagoscopy – preferred if possible, and (d) 24 hr pH-impedance with manometry in select cases to exclude gastroesophageal reflux disease (GERD).

14.4.2 VOMITING

Vomiting, i.e. *forceful expulsion of gastric contents with nausea or retching*, is a protective reflex, controlled by central emesis centers, which should be differentiated from regurgitation-an effortless involuntary event without nausea or retching.

Emesis *centres* are located in medulla and stimulated either directly by neurogenic afferents from GIT or indirectly by chemical stimuli from nearby chemoreceptor trigger zone (CTZ). Efferent response involves sudden violent descent of diaphragm and contraction of abdominal muscles to increase intra-abdominal pressure, with relaxation of cardiac sphincter to expel gastric contents.

Etiology: Occasional episodes of self-limiting vomiting are common in infancy due to *possetting*, *overfeeding* or *aerophagia*. A vomiting is likely to be pathological in presence of following *Red-flag signs*-(a) persistent or recurrent vomiting, (b) associated diarrhea, constipation or abdominal pain/distension, (c) associated fever, respiratory distress, altered sensorium or seizures, or (d) presence of bile or blood in vomitus **(Table 14.3)**.

Diagnostic evaluation aims to identify the etiology as well as consequences of vomiting, e.g. dehydration, dyselectrolytemia and growth failure in persistent/recurrent cases. *Metabolic alkalosis with hypochloremia* is commonest electrolyte abnormality due to loss of acidic gastric juices in vomiting. Important diagnostic clues include:
- *Age of onset:* Vomiting in *newborns* is a warning for congenital gut anomalies or neonatal sepsis after excluding benign causes, e.g. possetting, aerophagia or overfeeding. *Infants* with recurrent vomiting must be investigated for GERD, pyloric stenosis and inborn

TABLE 14.3: Causes of acute *or* persistent vomiting

	Acute vomiting	*Persistent vomiting*
Intestinal		
Esophageal	Foreign body, erosive esophagitis	GERD, foreign body, achalasia
Diaphragmatic	–	Eventration, hiatus hernia
Gastric	Acute gastritis—viral/drug induced	Peptic disease, IHPN, bezoars
Intestinal	Acute intestinal obstruction, NEC	Chronic obstruction, malrotation, worms
Visceral	Acute appendicitis, pancreatitis	Chronic pancreatitis, CIBD
Peritoneal	Acute peritonitis	Chronic peritonitis
Hepatic	Viral hepatitis, acute cholecystitis	Chronic liver disease, choledochal cysts
Extraintestinal		
Neurological	CNS infections, cerebral edema	ICSOL, hydrocephalus, migraine
Genitourinary	UTI, acute nephritis	Uremia, RTA, chronic UTI
Metabolic	Reye syndrome	IEMs, e.g. galactosemia
Endocrinal	Diabetic ketoacidosis	Adrenal insufficiency (CAH)
Drugs	Aspirin, quinines, digoxin, steroids	Anti-cancer drugs, radiotherapy
Poisoning	Food poisoning	Heavy metal poisoning
Others	Post-nasal drip, motion sickness	Whooping cough, food allergy

GER: Gastroesophageal reflux; **IHPN:** Infantile hypertrophic pyloric stenosis; **NEC:** Necrotizing enterocolitis; **CIBD:** Chronic inflammatory bowel diseases; **ICSOL:** Intracranial space occupying lesion; **RDS:** Riley-Day syndrome; **CAH:** Congenital adrenal hyperplasia; **IEM:** Inborn errors of metabolism

errors of metabolism. In *older children*, viral or drug-induced gastritis is the leading cause of vomiting apart from surgical abdominal emergencies, viral hepatitis, CNS infections, urinary tract infections, etc.

- *Onset and course:* Sudden onset of vomiting is usually due to local causes, e.g. viral or drug-induced gastritis or intestinal obstruction; while recurrent/persistent episodes indicates systemic pathology, e.g. raised intracranial pressure (ICP), hepatorenal disease or metabolic disorders. Recurrent vomiting with normal intervening period may also suggest cyclical vomiting syndrome or abdominal migraine.
- *Force, e.g.* forceful projectile vomiting indicates raised ICP or pyloric stenosis.
- *Diurnal/postural variations,* e.g. early morning vomiting episodes may be due to raised ICP, while tendency to vomit in recumbent position indicates possible GERD.
- *Relation with feeds:* Vomiting during or immediately after feeds indicates esophageal obstruction, while a delay of 15–20 minutes is common in pyloric stenosis. Vomiting due to extra-intestinal causes is not related to feeds.
- *Contents:* Presence of undigested food or fresh blood indicates upper GIT pathology, while bile indicates post-duodenal obstruction. Vomitus is highly foul-smelling in colonic obstruction and may contain fecal matter. Persistent, large, watery vomiting may also be due to rare *Zollinger-Ellison syndrome*.
- *Preceding/comorbid events*, e.g. headache, infection, drug ingestion, dietary intake, worm infestation, diarrhoea/constipation, foreign body and similar family history (food poisoning, migraine, metabolic defects) provide vital diagnostic information.
- *Physical examination* helps in etiological diagnosis, with presence of *icterus* in viral hepatitis, *abdominal tenderness* in surgical causes, *neurological signs* or papilledema in raised ICP; as well as to assess complications, e.g. dehydration, electrolyte disturbances, failure to thrive. Failure to thrive indicates chronic cause, e.g. infections, subacute obstruction and metabolic disorders.

Relevant investigations are necessary for etiological diagnosis as well as to assess fluid and electrolyte status. Important investigations in persistent vomiting include-urine analysis, liver/renal functions tests and abdominal ultrasonography, followed by CSF examination, esophagoscopy and metabolic screening in selected cases.

Differential diagnosis of common causes of vomiting in childhood include:

- **Possetting,** i.e. effortless recurrent regurgitation of gastric contents, reflects developmental immaturity of cardiac sphincter in early infancy to prevent backflow of gastric contents. Babies often outgrow it by 7–8 months and no intervention is required except burping after each feed.
- **Esophageal obstruction** (foreign body or strictures) presents with vomiting soon after feeding and contains recently ingested undigested food. Liquid are better tolerated than semi-solids.

- **GERD:** Vomiting is more common in lying down position and semisolids are better tolerated than liquids (Ch 14.6.2).
- **Food poisoning** often involves other members of family/group and diarrhea is common.
- **Infantile hypertrophic pyloric stenosis (IHPS)** is associated with typically projectile and non-bilious vomiting after 15–20 minutes of feeds, along with a mass, which is visible after feeds and disappears after vomiting (Ch 14.8.1).
- **Cyclic vomiting** refers to stereotypic episodes of intense nausea and vomiting with normal intervening period (see below).
- **Intestinal obstruction:** Vomiting is usually bilious, associated with abdominal distension and constipation. (Ch 14.13)
- **Raised ICP** in neurological disorders leads to early morning projectile vomiting, associated with headache, which is relieved after vomiting. Paroxysmal vomiting with preceding headache indicates migraine.
- **Rumination** denotes recurrent regurgitation of recently ingested food with subsequent spitting/remastication and swallowing. Self-induced vomiting is seen in adolescent girls with anorexia nervosa or bulimia.

Management of vomiting includes:

- *Symptomatic antiemetic therapy,* preferably with Domperidone (PO 0.3 mg/kg/dose) or Ondansetron (PO/IV 0.15–0.3 mg/kg/dose).

  Antiemetic drugs act by suppression of CTZ or facilitation of gastric emptying and include- (a) Dopamine antagonists, e.g. metoclopramide or domperidone; or (b) Serotonin-3 antagonists, e.g. ondansetron or granisetron. Other antiemetics, e.g. CTZ suppressors (prochlorperazine) or Antihistamines, (promethazine) are not used in children due to high risk of extrapyramidal reactions and sedation respectively.
- Correction of fluid and electrolyte imbalance.
- Evaluation of primary cause and its treatment.

Cyclic vomiting: Most cases have onset in pre-school or school age (> 2 years of age) and family history is present in 30–40%. Exact cause is unknown but each episode usually begins with autonomic features, e.g. lethargy, tachycardia, hypertension and abdominal pain.

Diagnostic criteria includes: (a) minimum total 5 episodes or 3 episodes in 6 months, (b) each episode lasting from 1 hour to 10 days with at least one week normal interval, (c) > 4 vomiting/hour for at least one hour, and (d) no identifiable cause.

Management includes antiemetics and supportive therapy during the episode, which can be prevented with Cyproheptadine (PO.25–0.5 mg/kg/d q8–12hr) or Propranolol (PO 0.25–1 mg/kg/d at bed time.

14.4.3 ABDOMINAL PAIN

Abdominal pain is a very common complaint in childhood, though may not be recognized in infants. Sudden coiling-up of body with abdominal rigidity, excessive crying and anxious, restless appearance may be a sign of abdominal pain in young children.

Abdominal pain may arise from somatic tissues or internal viscera. Visceral pain indicates spasm, distension, inflammation or ischemia of these organs and may be referred from or to other sites, e.g. abdominal pain due to basal pneumonia or right shoulder pain from the gallbladder.

Etiology: Abdominal pain may be acute *or* recurrent and idiopathic *or* secondary to identifiable cause **(Table 14.4)**.

Acute abdominal pain is usually organic in origin and needs exclusion of surgical/medical emergencies, specially if—(a) lasts for >3 hours, (b) well-localized or (c) associated with abdominal tenderness, distension, vomiting, fever or sick appearance. However, mild, short-duration, colicky pain is common in children and tends to be benign.

Recurrent abdominal pain (RAP), defined as *at least one episode per month for minimum three consecutive months*, is complained by 10–20% of children, of which ~70–80% are functional or psychological. It is often, but not always, possible to differentiate functional RAP from organic causes **(Table 14.5)** to avoid unnecessary investigations.

Functional RAP is uncommon below 5 years of age and tends to be more common in females, first-born children and those with timid or anxious personality. These children often find it difficult to describe or localize the pain and are usually normal in between attacks. Any stress in family or school may precipitate these attacks. Many functional disorders associated with abdominal pain have been described, as follows:

- *Irritable bowel syndrome (IBS),* defined as abdominal pain for at least one day per week in last 3 months, with any one of the following features during the episode: (a) pain related to defecation, (b) change in frequency of stools, and (c) change in consistency of stools (*Rome IV criteria*). Onset of symptoms must be at least 6 months before diagnosis.
- *Abdominal migraine* presents with paroxysmal episodes of intense abdominal pain, lasting for at least one hour with normal intervening periods of weeks/months *and* presence of any two of the following associated features – nausea, vomiting, anorexia, headache, photophobia and pallor.
- *Functional dyspepsia* denotes any one of the following for at least four times in a month for 2 months with- (a) post-prandial fullness, (b) early satiety, (c) epigastric pain.
- *Functional abdominal pain-not otherwise specified* (FAP-NOS), refers to episodic or continuous periumbilical

TABLE 14.4: Causes of abdominal pain

		Acute abdominal pain	*Recurrent abdominal pain (>3 months)*
a.	**Non-organic**	Dietary indiscretion, aerophagia	Infantile colic, psychological
b.	**Intra-abdominal**		
	• Esophagus	Acute esophagitis	Reflux esophagitis (GER, hiatus hernia)
	• Stomach	Acute gastritis (drug or viral)	Peptic ulcer (*H. pylori* infection), bezoars
	• Intestines	AGE, AIO, strangulated hernia	Constipation, worms, MAS
	• Liver	Hepatic abscess, cholecystitis	Gallstones, choledochal cysts
	• Pancreas	Acute pancreatitis	Chronic pancreatitis, pseudocyst
	• Peritoneum	Acute peritonitis, ischemia (SCD)	Koch's abdomen, gross ascites
	• Kidney	UTI, Dietel's crisis	Wilms' tumor, stones, chronic UTI
	• Spleen	Traumatic rupture	Gross splenomegaly
	• Pelvic disease	Testicular torsion	PID, Ovarian cyst
c.	**Somatic**	Trauma, infections	Non-specific myalgia
d.	**Extra-abdominal**	Non-specific myalgia	
	• Respiratory	Basal pneumonia, pleurisy	–
	• Cardiac	Rheumatic fever, pericarditis	–
	• Neurological	–	Abdominal epilepsy, migraine
	• Metabolic	Hypoglycemia	Porphyria
	• Spinal	Trauma	Tumor, Pott's spine
	• Endocrinal	Diabetic ketoacidosis	Hyperthyroidism, Addison disease
	• Poisoning	Ac. drug/chemical ingestion	Lead poisoning
	• Hematological	Sickle cell disease, porphyria	Tumors and lymphomas
	• Collagen disorders	Henoch-Schonlein purpura	–

AGE: Acute gastroenteritis; **AIO:** Acute intestinal obstruction; **GER:** Gastroesophageal reflux; **MAS:** Malabsorption syndrome; **PID:** Pelvic inflammatory diseases; **UTI:** Urinary tract infection.

TABLE 14.5: D/D functional vs organic RAP

	Functional	*Organic*
Age of onset	>5 years	<5 years
Location	Diffuse/Periumbilical	Localized
Character	Non-specific	Specific
Duration	>2 months	–
Symptoms at rest	Absent	Present
Effect on activity	None	Present
Assoc. findings	None	Present

pain at least four times in a month for >2 months, which does not fulfil criteria for IBS, Abdominal migraine or functional dyspepsia. Treatment includes reassurance, high-fiber diet, avoidance of carbonate drinks/refined food and psychotherapy.

Diagnostic evaluation of abdominal pain includes:

- ***Detailed history*** about its—(a) *onset, duration and progression*, (b) *character* (colicky, dull, burning, sharp shooting), (c) *localization** (epigastric, supraumbilical or infra-umbilical), (d) any *migration or change* in its character and severity, (e) *relationship with feeding, respiration and movements* and (f) *associated complaints*, e.g. vomiting, diarrhea/constipation, worm infestation, pica, urinary complaints and abdominal trauma, etc. Menstrual history is important in pubertal girls.

  **Pain arising from stomach, upper bowel, hepatobiliary system and pancreas is often localized in epigastrium. Periumbilical pain, common characteristic in appendicitis, also indicates distal bowel, cecal or proximal colon disease. Distal colonic, pelvic and bladder pain is usually suprapubic in location.*

- ***Clinical examination*** for abdominal distension, tenderness, rigidity or guarding, ascites, organomegaly, lump, bowel sounds, etc., along with examination of hernial sites, genitals and spine. Examination of lungs (basal pneumonia), heart (CCF/pericardial effusion) and rectal examination for pelvic inflammatory disease (in adolescents) is necessary to exclude extra-intestinal causes.
- ***Baseline investigations*** are necessary even in apparently functional cases to exclude organic pathologies and include:
  - Complete hemogram
  - Stool exam, specially for parasites and occult blood

  - Urine exam, specially for pus cells and crystals
  - Chest skiagram for basal pneumonia, TB, etc.
  - Tuberculin test
  - X-ray abdomen for obstruction, stones, etc.
- ***Relevant investigations:*** Ultrasonography is highly informative and essential investigation in all cases of unexplained/recurrent abdominal pain. Other investigations, e.g. contrast studies, CT/MRI or endoscopies are necessary only in selected cases.

Differential diagnosis of some important causes of organic abdominal pain is as follows:

- **Esophagitis or gastritis** presents with retrosternal pain with burning character, frequently associated with history of drug intake or viral infection.
- **Intestinal obstruction** may be acute or subacute and associated with vomiting, constipation and distension.
- **Acute appendicitis** begins in periumbilical pain, which slowly migrates to right ileac fossa after 4–6 hours. Rebound tenderness at *McBurney's point* is characteristic.
- **Biliary colic** is rare in children and generally presents with pain referred to right scapula or back. Intermittent colic with jaundice is a strong indicator of gallstones, specially in hemolytic anemia.
- **Ureteric or renal colic** typically begins in lumbar region and descends from loin to groin. Urinary retention for variable period during these episodes is common.
- **Dietel's crisis** presents with severe intermittent pain and oliguria, followed by polyuria after torsion of ectopic kidney is relieved.
- **Pelvic inflammatory diseases** are common in sexually active adolescents, best diagnosed on rectal examination.

14.4.4 CONSTIPATION

Constipation is a relative term as frequency of defecation varies significantly in different children. For practical purpose, *passage of hard stools every third day or even at lesser frequency* may be termed constipation. Constipation lasting for more than 4 weeks is considered as *chronic constipation*.

Defecation is largely a reflex activity in infants, before gradual development of voluntary control. Reflex is initiated by the distension of rectum by faeces sending afferent stimuli to spinal defecation centers at S_{2-4} followed by efferent parasympathetic impulses to relax anal sphincter.

Voluntary control by higher centres generally develops by 18 months, when defecation may be initiated or inhibited using abdominal and diaphragmatic musculature to alter abdominal pressure and anal tone.

Etiology: Constipation may be functional or organic **(Table 14.6)**. Organic constipation may arise from: (a) filling, (e.g. starvation, ileus) or evacuation, (e.g. anal fissures) defects in rectum, (b) impaired defecation reflex (Hirschsprung disease, spinal lesions), or (c) lack of effective contraction due to hypotonia of voluntary muscles.

TABLE 14.6: Causes of constipation

Non-organic
- *Habitual (functional):* Faulty toilet training
- *Low fecal load:* Under-feeding, low fiber diet
- *Dehydration:* Top feeding, poor water intake

Organic
- Dehydration: Fever, polyuria (Diabetes mellitus/insipidus)
- Mechanical: IHPS, AIO, anorectal anomalies
- Poor evacuation reflex: Hirschsprung disease
- Painful defecation: Anal fissure, hemorrhoids
- Hypotonia
  - General—hypothyroidism, floppy child, C. palsy
  - Local—spinal lesions, paralytic ileus, hypokalemia
- *Drugs:* Iron, laxative abuse, antihistaminics

IHPS: Infantile hypertrophic pyloric stenosis, **AIO:** Acute intestinal obstruction.

Anal fissures, Hirschsprung disease and hypothyroidism are three most common causes of organic constipation, except in early infancy when mild anorectal malformations have to be excluded.

Constipation tends to be *self-perpetuating*, with hardening of stools due to excessive retention in colon, making act of defecation further painful with voluntary retention. Eventually, watery colonic contents may percolate around hard-retained stools (*fecoliths*) and leak through anal sphincter, leading to *encopresis*.

Functional constipation is defined as persistence of constipation for >4 weeks with any two or more of following features: (a) stool frequency ≤2 per week, (b) hard, painful bowel movements, (c) excessive retention of stools, (d) large diameter stool obstructing the Indian pots, (e) faecal incontinence, (f) faecal mass or fecoliths on abdomen/rectum examination (*IAP 2018*).

Faulty and coercive toilet training, changes in the diet, acute illness or lack of clean toilet are important causes of functional constipation in children.

Diagnostic evaluation of constipation involves:

- *Age of onset:* Functional constipation often begins after 2 years of life
- *Clinical evaluation* for possible organic cause, as indicated by presence of intermittent diarrhea, significant abdominal distension and failure to thrive.
- *Stool examination:* Hard pellet or ribbon-like stools indicate Hirschsprung disease.
- *Per-rectal examination* to assess for anal position (anorectal malformations), fissures, anal tone (lax in spinal lesions), rectal findings (empty in Hirschsprung disease, fecoliths in functional constipation) and gush of fecal matter after withdrawal of finger (Hirschsprung disease).

- *Exclusion of hypothyroidism* by bone age estimation and serum TSH levels.
- Anorectal manometry for suspected Hirschsprung disease.

Treatment of organic constipation depends on the cause, while functional cases are treated with: (a) Regular *toilet training*, (b) *high-fiber diet* (0.5 g/kg/day) with adequate water intake, (c) *faecal disimpaction, and* (d) *oral laxatives.* Anal fissures, if there, must be treated.

Faecal disimpaction is indicated in acute severe cases with PO polyethylene glycol (25 ml/kg/hr for 4–6 hours) or per-rectal enema (sodium phosphate enema 2.5 ml/kg > 2 years). Saline enema is used in young infants.

Oral laxatives are indicated in sub-acute or chronic cases after excluding an obstructive pathology. Polyethylene glycol (0.5–1 gm/kg/day q12–24hr) is the preferred laxative of choice in children, though other osmotic laxatives, e.g. lactulose (1–3 ml/kg/day q12–24 hr) or Lactilol (200–400 mg/kg/day q12–24 hr) may also be used. Laxative therapy should be continued for many weeks before slow tapering.

Oral stimulant laxatives, e.g. Sodium picosulfate (10–20 mg/day q24 hr) or Bisacodyl (5 mg/day > 3 yr of age) may be used as *rescue therapy* for 2–3 days in patients on osmotic laxatives with intermittent exacerbations.

14.4.5 GIT BLEEDING

GIT bleeding may be broadly divided into three categories:

a. *Hematemesis*, i.e. blood-mixed vomitus containing either *fresh blood* suggestive of oropharyngeal, esophageal or gastric bleeding, or *altered blood* due to acid hematin formation in gastric bleeding.
b. *Melena*, i.e. dark tarry stools containing altered blood suggestive of upper GIT bleeds after a few hours, due to downward passage of blood.
c. *Hematochezia*, i.e. passage of fresh blood in stools, suggestive of colorectal or anal bleed.

Etiology: GIT bleeding indicates either a local pathology or a systemic bleeding diathesis **(Table 14.7)**. Esophageal varices or drug-induced gastritis are predominant causes of hematemesis and melena, while hematochezia usually indicates local pathology, e.g. anal fissures.

Diagnostic evaluation of GIT bleeding depends on the clinical presentation—hematemesis, melena or hematochezia. Other important etiological clues include:

- ***Detailed history,*** specially regarding-age of onset, coexisting abdominal pain, diarrhea, constipation or painful defecation, recent drug ingestion or worm infestation and past history of similar attacks.
- ***Physical examination*** specially for signs of nasal/dental bleed, portal hypertension, abdominal tenderness, anal fissure as well as sepsis or bleeding diathesis, e.g. purpura. In cases of massive bleeds, it is important to assess the severity of anemia (pallor) and circulatory insufficiency (hypotension/shock).
- ***Relevant investigations*** depending on probable site of bleed and include:
  - Endoscopy, i.e. esophagoscopy (for hematemesis) and proctoscopy/colonoscopy (for hematochezia) in severe or persistent unexplained bleeding.
  - Stool exam for occult blood and ova/cysts.
  - Plain/contrast radioimaging studies, specially to identify small intestinal causes – a region not easily accessible through endoscopes.
  - Screening for bleeding disorders, e.g. BT/CT, platelet count, coagulation profile, etc.
  - Sepsis screening, including blood cultures in suspected septic cases.

Table 14.7: Causes of GIT bleeding

A. Swallowed blood: Maternal*, epistaxis, caries	
B. Upper GIT bleed: (Hematemesis/ Melena)	
– *Esophageal*	: Varices, esophagitis, foreign body
– *Gastric*	: Acute gastritis, stress/peptic ulcer Mallory-Weiss syndrome
C. Lower GIT bleed (Hematochezia)	
– *Intestinal*	: Dysentery, IBD, NEC*, intussusception Meckel's diverticulum#, milk allergy#, Hookworm infestation#
– *Anorectal*	: Fissures, hemorrhoids, polyps, trauma
D. Systemic	: HDN*, septicemia, DIC, ITP, HSP.

IBD: Inflammatory bowel diseases, **HSP:** Henoch-Schönlein purpura
HDN: Hemorrhagic disease of newborn, **ITP:** Idiopathic thrombocytopenic purpura
*common causes in newborns, #occult bleeding.

Differential diagnosis of common causes of GIT bleeding are as follows:

- *Swallowed blood* is usually miniscule in amount, with prior history of epistaxis or gingival bleeding.
- *Esophageal bleeding* usually presents with sudden, large vomiting of fresh blood without gastric contents. Esophageal varices due to portal hypertension are the commonest cause of recurrent hematemesis. Retrosternal burning pain may be present in early cases.
- *Gastric bleeding* is common after ingestion of drugs, e.g. chloroquine or NSAIDs, and contains undigested food. *Mallory-Weiss syndrome* denotes hematemesis due to longitudinal mucosal tear at gastroesophageal junction or gastric cardia, following forceful vomiting/retching, irrespective of cause.
- *Meckel's diverticulum* is the commonest cause of recurrent painless hematochezia/melena, though abdominal pain may be present.

TABLE 14.8: Causes of abdominal distension

- ***Physiological:*** Obesity, constipation
- ***Hypotonia:*** PEM, rickets, hypothyroidism
- ***Fluid:*** Ascites, peritonitis
- ***Gaseous distension:***
  - Aerophagia (swallowed air)
  - *Malabsorption:* Lactose intolerance, gastroenteritis
  - Stasis, e.g. intestinal obstruction, paralytic ileus
- ***Intra-abdominal solids:***
  - Intestinal, e.g. fecoliths, Hirschsprung disease
  - Hepatosplenomegaly
  - Tumors

- *Hookworm infestation* is the commonest cause of occult bleeding in Indian children, while cow-milk allergy is common in infants.
- *Intestinal polyps* lead to painless bleeding which is rarely severe. *Peutz-Jeghers syndrome* is an autosomal disorder, characterized by intestinal polyposis and perioral pigmentation.
- *Anal fissures* are the commonest cause of painful hematochezia, associated with constipation.

14.4.6 ABDOMINAL DISTENSION

Abdominal distension indicates either hypotonia of abdominal musculature (Pot belly) *or* increased intra-abdominal pressure due to fluid, gas or organomegaly- often referred as 4 Fs, i.e. *f*at, *f*luid, *f*latus and *f*eces **(Table 14.8)**. A 5th F, i.e. *f*etus may be considered in adolescent females.

Acute intestinal obstruction is the most important cause of sudden abdomen distension in childhood, while gradually progressive distension usually indicates ascites.

Pot belly is a common cause of distended abdomen in Indian toddlers due to malnutrition or rickets, which needs to be distinguished from serious pathologies.

14.4.7 ABDOMINAL MASS/LUMP

Abdominal masses in children may arise from any visceral organ; best identified according to their location **(Table 14.9)** as well as associated complaints.

Local examination of mass for location, size, surface, consistency, tenderness, ballotability (renal masses) along with per rectal examination in pelvic masses, often limits the diagnostic possibilities. Presence of *hypertension* is an important clue towards renal mass.

Although the choice of investigations depends on probable cause, ultrasonography is a baseline investigations in most cases, apart from urine and stool examination. CT/MRI and radionucleotide scan may be required in selected cases.

TABLE 14.9: Causes of abdominal mass/lump

Right hypochondrium (hepatobiliary)
- Hepatomegaly
- Liver abscesses and cysts
- Liver tumors (primary/secondaries)
- Choledochal cysts, hydrops

Left hypochondrium (splenic)
- Splenomegaly/cysts
- Renal masses (see below- Lumbar mass)

Mid-abdominal (peri-umbilical)
- Infantile hypertrophic pyloric stenosis
- Intestinal—volvulus, intussusception, duplication
- Mesenteric—cysts, lymphadenoapthy
- Pancreatic—pseudopancreatic cysts

Lumbar (renal)
- Congenital anomalies, e.g. polycystic kidney
- Hydronephrosis
- Renal vein thrombosis
- Wilms' tumor

Suprapubic
- Full bladder
- Uterine mass, e.g. hydrometrocolposis
- Sacroccygeal teratoma

Iliac region
- Fecoliths
- Appendicular abscess (Rt side)
- Ovarian tumors or cyst
- Pelvic inflammatory diseases

14.5 DISORDERS OF ORAL CAVITY

Various structures of oral cavity participate in sucking, biting, chewing, lubrication and swallowing of ingested food, which is also primed for digestion by various salivary enzymes, e.g. amylase or lingual lipase. While sucking mechanisms are well developed at birth in term newborns, swallowing matures slowly over 1–2 months leading to higher risk of aspiration in newborns. Chewing mechanisms usually matures by 6–8 months, by the time to start weaning.

14.5.1 CLEFT LIP AND CLEFT PALATE

Cleft lip and cleft palate (CLP) are two distinct but closely related developmental malformations of oral cavity with impaired development or fusion of facial processes.

Embryology: Normally, the lip and alveolus develop by fusion of maxillary and medial nasal processes, while palate develops by fusion of two palatal halves in midline. Thus, *Cleft lip* represents absence of fusion between medial nasal process with maxillary process, while *cleft palate* indicates failure of two palatal shelves to approximate or fuse.

Incidence of cleft lip with/without palate and cleft palate alone is ~ 1:1000 and ~1:2000 children respectively, former being more common in males. Isolated cleft palate is more common than isolated cleft lip (40% *vs* 15%), while ~45% cases have combined defect.

Fig. 14.3: **Cleft lip (A) and cleft palate (B).**

Cleft lip is usually an isolated defect, while cleft palate may be either alone or with other congenital malformations, e.g. first branchial arch defects or chromosomal abnormalities.

Etiology of CLP is multifactorial with a genetic basis and environmental factors, e.g. maternal smoking or alcohol/drug consumption. Familial tendencies are known, with recurrence risk of ~3–4% and ~10–15% in siblings and offsprings of the index case, respectively. Many genetic mutations have been identified associated with CLP, e.g. TGFA, TGF-133, etc.

Clinically, cleft lip may be unilateral or bilateral, varying from being a small notch in vermillion border to complete separation extending up to nasal floor. Cleft palate may involve uvula, soft and hard palate or even combine with cleft lip to expose one or both nasal cavities **(Fig. 14.3)**.

Functionally, cleft lip alone is a cosmetic abnormality, while cleft palate can adversely affect various facial functions e.g,

- Feeding difficulties, due to inability to create sufficient negative pressure for sucking.
- Recurrent aspiration and respiratory infections
- Deafness, due to eustachian tube dysfunction and recurrent otitis media.
- Dental malocclusion and caries.
- Speech defects, due to misarticulation, hyper/hyponasality and nasal escape.

Management of CLP is a team-work involving surgeon, dentist, pediatrician and speech therapist. Treatment of cleft lip is mainly surgical, while cleft palate requires special medical care till repaired.

Medical management of cleft palate includes:

- *Feeding:* While many babies with cleft palate can suck effectively, it is preferable to feed them expressed breast milk via a bondla or spoon to obviate the need of sucking and in propped-up position to prevent aspiration. *Obturators* may be useful to allow direct breastfeeding in smaller clefts.
- *Speech* often remains impaired till surgery, but subsequently normal speech may be attained after surgery by speech therapy.
- *Dental malocclusion* requires post-operative orthodontic correction. Normal jaw growth and dental occlusion may remain subnormal even after surgery, due to abnormal compression of the repaired lip, inherent bony deficiency and scar contracture.
- *Hearing* is commonly impaired due to recurrent otitis media and hence, early treatment of these cases is critical to retain hearing and later speech.

Surgical management aims to aesthetically reconstruct the defect, to obtain adequate speech and feeding functions, and to encourage adequate growth of facial skeleton. Just after birth, pre-surgical orthodontics/nasoalveolar molding may be given to reduce the width of the cleft, correct the depression of the alar base and improve alveolar alignment.

- ***Cleft lip*** is usually operated at 3–6 months (Rule of 10-age: 10 weeks; Weight: 10 lb; Hb: 10 gm) with *Z-plasty*, though revision surgery may be needed at 5–6 years and rhinoplasty during adolescence.
- ***Cleft palate*** is usually operated at 9–12 months to allow normal speech development, though timing has to be individualized according to the size of defect. Good post-operative care is critical for surgical success, as wound infection with re-opening of defect and aspiration are common post-operative complications.

Some other important orofacial malformations are as follows:

Pierre-Robin syndrome is an important orofacial malformation with mandibular hypoplasia, characterized by a triad of—(a) micrognathia/retrognathia, (b) macroglossia, and (c) glossoptosis. These cases must be managed in prone position to prevent posterior displacement of the tongue that may obstruct airways. Severe cases may require suturing of the tongue with alveolar margins and/or tracheostomy, till mandibular growth is adequate.

Treacher Collins syndrome (Mandibulo-facial dysostosis) is a rare facial dysmorphism, with triangular face, receding chin, blind fistulas between ears and angle of mouth, downward slant of eyes, coloboma of eyelids and ear abnormalities with/without deafness.

14.5.2 DENTAL CARIES

Dental caries (*tooth decay*), is a very common problem in Indian children, involving mainly deciduous teeth.

Etiologically, caries may be divided into three steps:

a. Collection of residual carbohydrates over dental pits and between teeth, forming a *plaque.*
b. Fermentation of these plaques by acid-forming oral flora, e.g. *Strept. mutans,* lactobacilli, etc.
c. Demineralization and destruction of enamel by these acids.

Fig. 14.4: **Dental caries.**
(*Courtesy:* Dr Adesh Kakade)

Risk factors: Bottle-feeding, sticky candies, and enamel hypoplasia due to malnutrition or fluorine deficiency are three most important risk factors for caries, apart from others, e.g., poor oral hygiene, salivation disorders, GERD and family history.

Clinically, dental caries generally begins in *difficult to see* areas, e.g. pits,fissures or contact surfaces of two adjoining teeth, as an opaque white plaque that enlarges and deepens gradually to produce visible cavities. Presence of pain indicates spread of caries to the pulp.

Untreated caries may progress to develop more severe complications, e.g. (a) pulpitis, (b) dental abscess, and (d) neighbouring infections, e.g. gingivitis, facial cellulitis, Ludwig angina and osteomyelitis **(Fig. 14.4)**.

Treatment: Role of pediatrician in dental caries primarily involves: (a) early detection of lesions and timely referral to dentist, (b) control of pain/inflammation with analgesics and antibiotics, and (c) management of complications, apart from preventive guidance.

Prevention depends on: (a) maintenance of oral hygiene, (b) improvement of nutrition and avoidance of sweetened foods, (c) adequate fluoride content of water (minimum 1 ppm) and monitoring of high-risk cases. Use of topical fluoride agents or dental sealants is beneficial in some cases.

14.5.3 ORAL CAVITY INFLAMMATIONS

Oropharyngeal inflammations may be infectious *or* non-infectious in origin. Some common inflammatory disorders of oropharynx include:

Cheilitis, i.e. *inflammation of lips and angle of mouth* (angular cheilitis) is commonly caused by dryness in winter or windy weather, which may be treated with frequent application of petroleum jelly. However, severe/refractory cases may be due to—(a) zinc deficiency, (b) contact/atopic dermatitis, and (c) extension of oral thrush.

Aphthous ulcers *or* stomatitis present as solitary or multiple, well-circumscribed lesions of variable sizes, with gray fibrinous exudates and erythematous halo on gingival, lingual or palatal mucosa.

Etiology is probably multifactorial, thought may be associated with local trauma, vitamin B_{12} deficiency, emotional stress, malabsorption syndrome or allergy. Most cases improve spontaneously within 7–10 days and treatment is palliative with topical application of viscous xylocaine or steroids before feeding.

Severe/recurrent/persistent ulcers are seen in-(a) entero-viral infections, e.g. herpangina, hand-foot-mouth disease, (b) chemical/thermal burns, (c) gingivostomatitis due to anaerobic infections, and (d) systemic diseases, e.g. Crohn disease, Behçet's syndrome, SLE, etc.

Vincent angina (Trench mouth) is an acute, fulminant, necrotizing infection of oral cavity due to *anerobic* flora, e.g. fusobacteria and spirochetes. Mostly seen in severely malnourished children, these cases present with-(a) painful gingival ulceration and swelling, (b) adherent grayish pseudomembrane over affected gingival and (c) foul-smelling breath with/without signs of systemic infection. Treatment includes antibiotics (penicillin/erythromycin), local debridement and analgesics.

Oral thrush is very common in normal newborns or young infants <3 months. In older children, it may be seen in cases with—(a) prolonged antibiotic therapy, (b) chronic debility or immunodeficiency states.

Clinically, thrush appears as whitish patches over oral mucosa **(Fig. 14.5)**, with inflamed base that leaves pin-point hemorrhages on removal (*d/d* milk patch).

Topical nystatin or clotrimazole application is often enough, though severe/persistent thrush requires exclusion of immunodeficiency disorders and systemic

Fig. 14.5: **Oral thrush.**

antifungal therapy. Oral rinses with 0.2% chlorhexidine may be useful to prevent recurrence, specially in immunocompromized cases.

14.5.4 TONGUE DISORDERS

Common tongue disorders include abnormalities of its size or appearance, which may/may not be of clinical consequence.

Macroglossia is seen in hypothyroidism, Down syndrome, Beckwith syndrome, Pierre Robin syndrome and tongue hemangioma.

Abnormal appearance, e.g. *geographic tongue* (single/multiple, well-demarcated, smooth red plaques due to transient papillary atrophy), *scrotal tongue* (deep fissured tongue with wrinkled appearance), *black hairy tongue* (dark-coated tongue with papillary hyperplasia) may be idiopathic or secondary to infection, malnutrition, atopy or trauma. No treatment is needed in these cases, except to ensure adequate oral hygiene, nutrition and control of infection, if present.

14.5.5 SALIVARY GLAND DISORDERS

Salivary gland abnormalities may involve one or more of three salivary glands—parotids, submandibular or submental glands.

Acute parotitis is almost always caused by mumps (usually bilateral), though needs to be differentiated from rare case of *acute suppurative parotitis* in staphylococcal infections (unilateral), or other causes of *parotid enlargement*, e.g. malnutrition, HIV infection, cystic fibrosis and benign salivary gland hypertrophy.

Xerostomia *(dry mouth)*, seen in any fever, dehydration, anticholinergic therapy and Sjögren's syndrome, may also precipitate parotid swelling/parotitis due to desiccation of salivary secretions in their ducts.

Ranula is a common cyst of major salivary gland (usually sublingual), presenting as a large, soft, mucus containing swelling over floor of the mouth at any age, which needs to be excised.

14.6 ESOPHAGEAL DISORDERS

Esophagus propels the swallowed food from oropharynx to stomach by peristaltic activity, as well as prevents regurgitation of gastric contents by tight closure of lower esophageal sphincter at rest. A sharp angulation between lower esophagus and gastric fundus also prevents regurgitation.

In newborns, developmental incompetence of lower esophageal sphincter and relative straightening of gastroesophageal junction may lead to transient gastroesophageal reflux, which improves with age.

Dysphagia, odynophagia and vomiting or regurgitation of gastric contents are common presentations in esophageal disorders.

14.6.1 TRACHEOESOPHAGEAL FISTULA (TEF)

Esophageal atresia (EA) with or without tracheoesophageal fistula (TEF) is a life-threatening surgical emergency in newborns, seen in ~1:3000–5000 live births and carries high mortality, unless operated within 24 hours of birth.

Embryogenesis: Esophagus and trachea develop from a common primitive foregut, separated by a tracheoesophageal septum. EA usually results from posterior deviation of this septum, while its incomplete development results in concurrent TEF. EA without TEF may also result from incomplete canalization of the primitive esophagus.

Other congenital anomalies are present in ~50% cases, including VACTERL association, i.e. ***V***ertebral, ***A***norectal, ***C***ardiac, ***T***racheo***e***sophageal fistula, ***R***enal/***R***adial and ***L***imb defects.

Pathogenesis: Due to blocked esophageal passage and fistulous communication, these babies develop regurgitation and aspiration of feeds or gastric secretions soon after birth, with chemical pneumonitis and subsequent secondary bacterial pneumonia.

Anatomical types: Various anatomical variations of these defects are as follows **(Fig. 14.6)**:

- *Type I* (85%): Most common type, in which a fistula connects lower end of esophagus with trachea while upper end of esophagus is blind.
- *Type II* (8%): Both, the upper as well as lower end of esophagus are blind with no fistula.
- *Type III* (4%) is an H-type fistula, with no EA but a connecting tract between trachea and esophagus, usually at the level of carina. Frequently missed at birth, these cases present in infancy with recurrent aspiration.
- *Type IV* (<2%): A fistulous connection between upper esophageal pouch and trachea, with blind lower end of esophagus.
- *Type V* (<1%): Two separate fistulous tracts between blind upper and lower ends of esophagus, with EA.

Clinically, all cases except H-type, present within a few hours of birth with:

- Persistent, copious, fine, white, frothy bubbles of mucus in mouth,
- Recurrent episodes of coughing, cyanosis and choking at the time of feeding with progressive respiratory distress due to aspiration pneumonia,

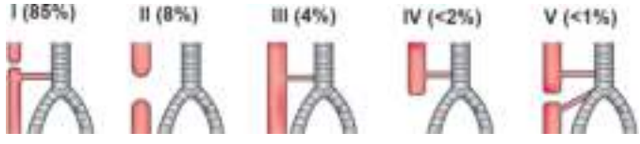

Fig. 14.6: **Anatomical types of TEF.**

- Progressive abdominal distension in type I, due to air passage from trachea to lower end of esophagus or *scaphoid abdomen* in type II/IV due to blind lower end.
- Failure or difficulty to pass a nasogastric tube at birth for gastric aspiration or feeding at birth.

Most of these babies are *preterms* and have history of maternal *polyhydramnios* due to impaired swallowing of amniotic fluid by fetus.

Children with *H-type fistula* are usually missed in neonatal period and present later with recurrent aspiration pneumonia.

Diagnosis: Early diagnosis of EA/TEF requires high index of suspicion, though routine check for esophageal patency after birth is not necessary in all newborns. Diagnosis may be confirmed by:

- *Plain chest and abdominal skiagram* after passing a nasogastric tube with radioopaque line to *see*—(a) the curled-up tube suggestive of blocked esophageal passage **(Fig. 14.7)**, (b) presence or absence of gas shadow in stomach, depending on whether lower end of esophagus is connected with trachea, and (c) presence or absence of aspiration pneumonia.
- H-type fistula is difficult to detect, although *milk scan and bronchoscopy* to *see* tracheal end of fistula or *video-esophagogram* may be useful.
- Abdominal USG and other relevant investigations are necessary to exclude associated anomalies.

Prenatal diagnosis is possible only in ~40% cases, which must be suspected in presence of maternal polyhydramnios and small or absent stomach bubble on USG. Fetal MRI is more reliable.

Treatment: EA/TEF should be operated as early as possible, at least within 24 hours of birth, before the development of aspiration pneumonia.

Pre-operative stabilization of these cases includes:

- Nursing in prone position to reduce the risk of aspiration,
- Continuous suction of the upper esophageal pouch,
- Maintenance of temperature and parenteral nutrition,
- Prophylactic antibiotics and
- Humidified oxygen or ventilatory support, if necessary.

Surgical options depends on the length of atretic esophageal segment and general condition of the patient, as follows:

- *Stable patients with small atretic defects* are usually taken for immediate corrective surgery with *trans-thoracic ligation of fistula with end-to-end esophageal anastamosis.* Oral feeding may be resumed after 8–12 days of primary anastamosis.
- *Sick children or those with long defects* are operated in two-stages-*initial gastrostomy* for decompression and later *primary repair,* which may require esophageal reconstruction surgery, using a gastric or colonic tube.

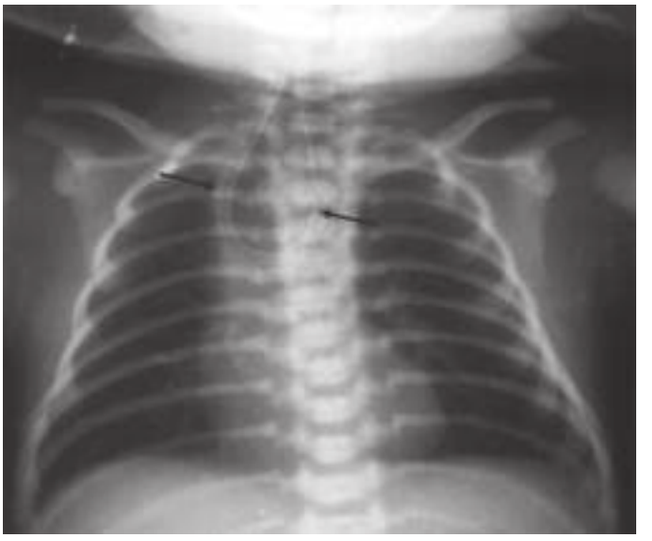

Fig. 14.7: Tracheoesophageal fistula
(*Note:* Arrows showing coiled-up nasogastric tube)

Outcome depends on the timing of surgery and presence of associated malformations. With first-day surgery before aspiration, survival rate is ~80%, though late complications, e.g. GERD or esophageal stenosis are common.

14.6.2 GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Gastroesophageal reflux disease (GERD) denotes *recurrent regurgitation of gastric contents into esophagus* due to any cause, leading to persistent esophagitis by regurgitant acidic gastric content.

Etiopathogenesis: Mild GER is common in first year of life and after meals in older children, with no clinical consequence. Pathological GERD may result from:

1. *Incompetence of lower esophageal sphincter* due to: (a) abdominal location of esophagus, (b) abnormal angle of its insertion into stomach, (c) hiatus hernia, (d) inappropriate transient relaxation of sphincter during swallowing, crying or after drugs, e.g. theophylline, or (e) nasogastric tube *in situ*.
2. *Increased intra-abdominal pressure*, due to chronic cough, constipation and other causes.

Clinical manifestations of GERD begin in early infancy with a triad of: (a) recurrent vomiting/possetting, (b) recurrent chest infections, and (c) failure to thrive. Signs of esophagitis, e.g. dysphagia or sub-sternal pain may not be obvious in infants, while hematemesis is rare.

GERD has been claimed to be associated with acute life-threatening events (ALTE) or sudden infant death syndrome (SIDS), due to sudden choking by aspirated contents.

Diagnosis may be confirmed by:

- *Milk scan* showing slow gastric emptying and reflux of radiolabel contents, fed before the scan. It is also useful

to identify severity of reflux. However normal milk scan does not exclude GER, which is an intermittent event.

- *24-hour esophageal pH probe monitoring* to demonstrate acidic pH at lower end of esophagus is the most reliable indicator of GERD, though rarely indicated in routine cases.
- *Esophageal manometry* is also useful to identify intermittent relaxation of lower esophageal sphincter.
- *Barium swallow or esophagoscopy* is indicated in chronic cases to visualize esophagitis, strictures and anatomical abnormalities, e.g. hiatus hernia.

Management of GERD depends on its severity and includes:

- *Positioning:* Nursing the baby in semi-upright position, especially after feeds and during sleep, to promote gravity assisted emptying of esophagus.
- *Feeding* with thickened feeds, given as frequent but small boluses.
- *Acid suppressors:* Proton pump inhibitors (PPIs), e.g. lansoprazole (PO 0.7–1.4 mg/kg/day q24hr), or Esopantoprazole (PO 1–2 mg/kg/day q24 hr), etc. are first drugs of choice for GERD with erosive esophagitis. Empirical PPI therapy may also be used for short trial of 4–8 weeks in symptomatic children beyond infancy. H_2 receptor antagonists, e.g. Rantidine, though provide faster relief, are less effective and indicated only if PPIs are contraindicated.
- *Antacids* may be used for temporary symptomatic relief, but prolonged use should be avoided in children. Surface protectors, e.g. Sucralfate or alginates are not recommended for routine management of GERD in children.
- *Prokinetic agents* to enhance gastric emptying, e.g. metoclopramide or Domperidone (Both 0.15–0.20 mg/kg/d q8hr) may be used in *moderately severe* cases.
- Surgery, i.e. *fundoplication* is indicated only in very severe cases, refractory to medical therapy. Commonly used *Nissen fundoplication* involves wrapping of gastric fundus around intra-abdominal esophagus to act as additional valve, with success rate of >90%.

Prognosis: Most cases of GERD outgrow it by the end of first year, though complications, e.g. esophageal strictures, severe GIT hemorrhage, chronic lung disease and failure to thrive are common. GERD is considered as a triggering factor for acute asthmatic exacerbations and an important cause of *Difficult-to-treat asthma* in children.

Some other important esophageal disorders are as follows:

Achalasia is an esophageal motility disorder characterized by paucity of normal peristaltic waves and impaired relaxation of gastroesophageal junction, due to decreased number or sensitivity of ganglionic cells. Only < 5% of all cases present in childhood.

Clinically, most cases present in adolescence, with swallowing difficulties and GERD, leading to chronic esophagitis, recurrent aspiration and chronic lung disease.

Diagnosis usually rests on barium swallow, which reveals esophageal dilatation with tapering towards gastric junction. *Esophageal manometry* is diagnostic, showing lack of peristaltic changes and relaxation of lower esophageal sphincter on swallowing.

Treatment is mainly surgical with *Heller myotomy* or endoscopic *balloon dilatation* of lower esophageal sphincter, though drugs, e.g. nifedipine may be effective in some cases. Intra-sphincteric injection of Botulism toxin (botox) has been found effective for 4–6 months.

Esophagitis in children may be: (a) *Peptic* due to GERD, (b) *Infective* (Candida, HSV), usually in immunocompromised children, or (c) *Corrosive*; the last being most common, caused by accidental ingestion of household substances, e.g. acids, alkalis, detergents, etc.

Clinically, vomiting, retrosternal burning and dysphagia are typical features of esophagitis and severe or persistent esophagitis may cause stenosis with chronic dysphagia.

Treatment depends on the cause, though nasogastric lavage or induction of emesis is contraindicated in cases of suspected corrosive poisoning (Ch 27.6).

Esophageal foreign body, e.g. coins ingestion, is common in toddlers due to their inquisitive nature. Ingested bodies are usually lodged at any one of three normal constriction sites in esophagus-below the cricopharyngeal muscle, at the level of aortic arch or just above the diaphragm.

Clinically, these cases may present immediately with suggestive history or later with dysphagia, more pronounced with solids. Radio-opaque bodies are visible on X-rays, though diagnosis of radiolucent ones requires barium swallow or preferably, endoscopy.

Treatment: All symptomatic cases or those with history of ingesting sharp foreign bodies need immediate endoscopic removal, while blunt foreign bodies like coin, single magnet may be observed for up to 14 days for spontaneous clearance, if asymptomatic.

14.7 DIAPHRAGMATIC DISORDERS

Diaphragmatic disorders are usually congenital, though acquired defects due to direct trauma or neurological injury (diaphragmatic palsy) are not uncommon.

14.7.1 CONGENITAL DIAPHRAGMATIC HERNIA

Congenital diaphragmatic hernia (CDH) denotes *'herniation of abdominal contents into the thoracic cavity* through an abnormal opening in diaphragm, e.g. posterolateral *foramen of Bochdalek* or antero-lateral *foramen of Morgagni'*.

Embryogenesis: Thoracic and abdominal cavities separate from each other by closure of posterolateral pleuro-peritoneal canals at 8th week of gestation. Failure of such closure leads to development of *Foramen of Bochdalek,* through which abdominal contents, usually a part of intestine, may herniate into thoracic cavity and compress the developing lung, leading to pulmonary hypoplasia and respiratory insufficiency of variable severity. Strangulation of herniated sac may also cause intestinal obstruction and sepsis.

Congenital anomalies, e.g. heart defects, esophageal/duodenal atresia, neural tube defects, renal anomalies, and chromosomal trisomies are present in ~20–30% cases.

Incidence: Diaphragmatic hernia is present in ~1: 2000 births. Most of them are on left side (70–85%). Bilateral hernia is seen in 5%, while isolated hernia through foramen of Morgagni is rare (<2%).

Clinical presentation depends on size of the hernial sac, severity of pulmonary hypoplasia and presence of associated anomalies.

A typical case presents in early neonatal period with-(a) progressive respiratory distress, (b) scaphoid abdomen, and (c) decreased breath sounds and presence of bowel sounds on affected side with shift of mediastinum on opposite side. Chest may be unusually prominent or bulging on affected side.

History of maternal polyhydramnios is common due to impaired absorption of amniotic fluid.

Children with smaller defects or herniation through foramen of Morgagni may present in later life with recurrent vomiting, respiratory infections and failure to thrive.

Diagnosis: Diaphragmatic hernia may be diagnosed prenatally on ultrasonography by 16–20 weeks. Postnatal diagnosis may be confirmed on *chest X-ray* showing-(a) presence of air-filled bowel loops on left side, (b) absence of the cupola of diaphragm on affected side, and (c) shift of mediastinum on opposite side **(Fig. 14.8)**. *Lateral view* may reveal intestines passing through the posterior portion of diaphragm.

Other useful investigations include *Barium* contrast studies to delineate the herniated bowel segments and *chest CT* to identify the severity of lung hypoplasia.

D/D: Radiological appearance is characteristic but may be rarely confused with-(a) pneumothorax, (b) staphylococcal pneumonia with pneumatoceles, (c) lung cysts and (d) eventration of diaphragm.

Management of diaphragmatic hernia is essentially surgical, involving reduction of herniated segment and repair of diaphragmatic defect, *as early as possible* after pre-operative stabilization.

Pre-operative stabilization requires – (a) nasogastric decompression, (b) fluid and electrolyte correction, and (c) ventilatory assistance after endotracheal intubation. *Bag and mask ventilation is contraindicated during resuscitation as air-distended herniated intestines may cause further respiratory embarrassment.*

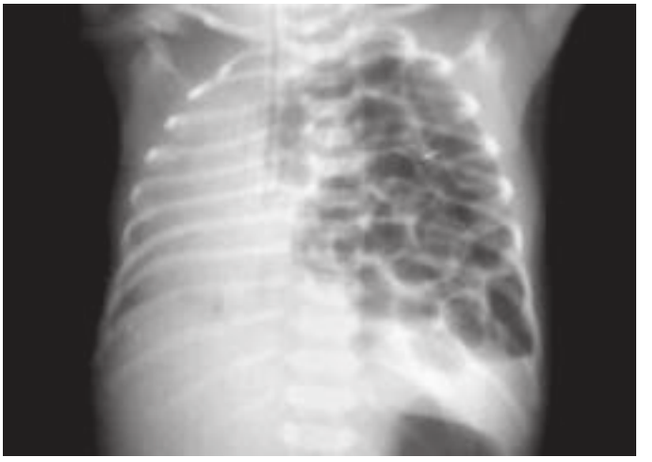

Fig. 14.8: Congenital diaphragmatic hernia.

Lung hypoplasia in these cases may lead to severe pulmonary hypertension with right to left shunt, which needs to be treated with vasodilators (dopamine, nitric oxide inhalation), surfactant and extracorporeal membrane oxygenation, if possible.

In antenatally diagnosed cases, *in utero* reduction of hernial sac or tracheal ligation to prevent egress of lung fluids and pulmonary hypoplasia, has been attempted.

Prognosis: Overall mortality is ~30–40%, being higher in cases with—(a) respiratory distress within 24 hours of birth, (b) severe lung hypoplasia, and (c) co-existing congenital anomalies. In operated cases, late effects like-(a) restrictive lung disease (b) GERD, (c) recurrence (~20–40%), and (d) thoracic cage deformities, (e.g. scoliosis) are common.

Other important diaphragmatic abnormalities are as follows:

Eventration, refers to *congenital hypoplasia of diaphragmatic muscles*, leading to elevation of entire hemidiaphragm *or* more commonly, the anterior crux into thoracic cavity. It is more common on left side.

Clinically, large eventration presents like diaphragmatic hernia with neonatal respiratory distress, while smaller defects may remain asymptomatic or manifest with recurrent chest infections in older children. Recurrent vomiting and abdominal pain after meals are common.

Diagnosis is established on chest X-ray, showing *'rainbow'* like elevation of diaphragm with smooth contour and *cloudy mottling appearance* of intestine below it **(Fig. 14.9)**. Fluroscopy may be useful to differentiate it from diaphragmatic hernia, showing paucity of diaphragmatic movements on affected side.

Fig. 14.9: **Eventration of diaphragm.**

Treatment involves *fundoplication* through abdominal or thoracic approach, though mild asymptomatic cases need no intervention.

Hiatus hernia denotes sliding or herniation of gastro-esophageal junction or a portion of stomach through normal or patulous esophageal opening in diaphragm, usually associated with severe GERD. Treatment is directed towards GERD and not for hernia. Patients with symptomatic giant hiatal hernias need surgical intervention.

14.8 GASTRIC DISORDERS

Stomach predominantly acts as a food-reservoir, though the process of digestion also begins here. Various digestive juices are secreted in stomach including hydrochloric acid and intrinsic factor by parietal cells, pepsinogen by chief cells and mucus as well as some hormones, (e.g. gastrin) by other specific cells.

Gastric acid (normal gastric pH 1–1.5) facilitates hydrolysis of proteins, conversion of ferric iron *into* ferrous form, and activation of pepsinogen into active pepsin. *Intrinsic factor of castle* is essential for vitamin B_{12} absorption. *Pepsin* initiates process of proteolysis, i.e. conversion of larger protein molecules into smaller peptides. Emulsification of fats and hydrolysis of triglycerides also begins in stomach, due to activation of *lingual lipase* and secretion of *gastric lipase*.

While gastric emptying starts soon after the entry of food, rate depends on the type of ingested food, with half-emptying time being ~15–20 minutes for liquids and ~90–120 minutes for solids.

Vomiting, hematemesis and abdominal pain are common manifestations of gastric disorders.

14.8.1 INFANTILE HYPERTROPHIC PYLORIC STENOSIS

Infantile hypertrophic pyloric stenosis (IHPS) denotes *narrowing of gastric outlet due to the unexplained thickening and hypertrophy of the pylorus muscle*, primarily the circular layers.

Incidence: IHPS is the commonest cause of gastric outlet obstruction (~1–4/1000 live births), more common in males (2–5:1), first-born babies and offspring of the parents (specially mothers) with history of IHPS.

Etiology: In IHPS, pyloric hypertrophy is minimal at birth and develops gradually over first few weeks. Many genetic, familial and environmental factors have been attributed for this hypertrophy, e.g. (a) curdled milk, leading to mucosal edema and secondary pyloric hypertrophy, (b) less number and maturity of ganglion cells, (c) elevated gastrin levels and (d) deficiency of nitric oxide in pyloric muscle.

Clinically IHPS usually manifests from 2nd to 3rd week of neonatal life with:

- Recurrent projectile vomiting of curdled milk, after 20–30 minutes of feeding. Vomiting is essentially non-bilious, occasionally streaked with blood, and increases gradually in frequency, amount and force. After vomiting, baby is hungry and wants to be fed again.
- Failure to thrive, dehydration and constipation due to persistent vomiting. Infant is typically anxious, anemic and irritable/lethargic.
- Abdominal examination may reveal *a firm, moveable, olive-shaped, supraumbilical lump on right side*, which can be rolled between fingers. Lump is better palpable from the left side and immediately after feeding. Visible peristalses from left to right side are common after feeds, to overcome obstruction **(Fig. 14.10A)**.

Fig. 14.10A: **Infantile hypertrophic pyloric stenosis: Abdominal lump.**

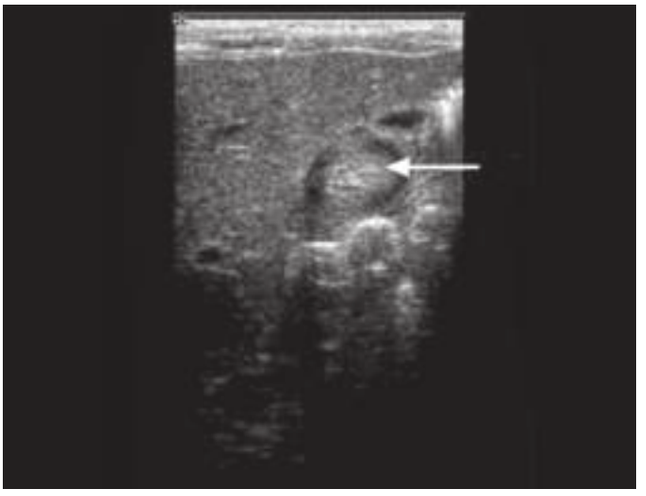

Fig. 14.10B: Infantile hypertrophic pyloric stenosis: Target (doughnut) sign on USG.

- Obstructive jaundice may develop in ~2%, due to pressure of hypertrophied pylorus on ampula of Vater.

Associated anomalies like Down syndrome, Turner syndrome and tracheoesophageal fistula may be present.

Diagnosis rests on typical appearance of pyloric lump, supported by:

- *Barium meal* showing—(i) long and narrow pyloric canal, (ii) *string sign*, i.e. passage of only a streak of barium, (iii) *double-track sign* due to crowding of mucosal folds in pyloric channel, and (iv) *Shoulder sign* due to bulging of pyloric muscles into antrum.
- Ultrasonography showing *Target (Doughnut) sign* due to hypertrophied ring of pyloric muscle around echogenic mucosa **(Fig. 14.10B)**. Pyloric muscle thickness of >13 mm and length of pyloric channel >17 mm on USG is pathognomonic.

Treatment: While these cases need surgery as early as possible, most of them are too sick at the time of diagnosis with dehydration and electrolyte disturbances and need to be stabilized before surgery.

Pre-operative management includes—(a) nasogastric decompression, (b) correction of dehydration/electrolyte disturbances and (c) IV alimentation.

Hypochloremic metabolic alkalosis is commonest electrolyte abnormality in IHPS, due to loss of chlorides in vomiting. Normal saline or N/2 dextrose saline with 30–50 mEq/L of potassium is preferred for initial parenteral therapy with close monitoring of urine output and serum bicarbonate levels. Untreated alkalosis also increases the risk of post-operative apnea.

Ramstedt's pyloromyotomy is the surgery of choice in IHPS, in which hypertrophied pyloric muscles are split without cutting the mucosa and spread apart till mucosa prolapses into the pyloric incision. Oral feeding may be initiated after 12–24 hours, though some vomiting due to pyloric wall edema may continue for a few days. *Laparoscopic pyloromyotomy* or *endoscopic balloon dilatation of pylorus* are other options.

TABLE 14.10: Causes of acute gastritis/ulcers

- *Drugs:* NSAIDs, iron, chloroquine, steroids
- *Septicemia:* Gm –ve infections, endotoxemia
- Dehydration/shock
- Severe hypoxia, e.g. acute respiratory failure
- *Cushing ulcers* – post-surgery, head injury
- *Curling ulcers* – burns

Other important gastric disorders are as follows:

Acute gastritis is usually caused by drugs, e.g. chloroquine or stress ulcers in critically sick children **(Table 14.10)** and presents with recurrent vomiting, epigastric pain and hematemesis in severe cases.

Treatment includes—(a) *Antacids*, (b) H_2 *receptor antagonists*, e.g. Ranitidine (4–6 mg/kg/day q12hr), (c) *Proton-pump inhibitors*, e.g. omeprazole, and (d) *mucosal-coating agents*, e.g. sucralfate.

Chronic gastritis *(peptic ulcer disease)* in children has been strongly correlated with *H. pylori* infections, though family history of peptic disease is present in 25–50% cases. *Zollinger-Ellison syndrome* is a rare cause of multiple duodenal ulcers and diarrhea, due to gastrin-producing islet-cell tumor of pancreas.

Helicobacter pylori is a gram-negative, *urease-producing* organism, which colonizes ~50% children by 10 years of age and lives in the mucus overlaying gastric antrum. Infection is acquired by man-to-man transmission via feces, vomitus, saliva, etc. in overcrowded and unsanitary conditions. Although frequently associated with duodenal ulcers, whether the organism causes the ulcer or simply prevents its healing, is unclear.

Clinically, most *H. pylori* infections in childhood are asymptomatic, though some may present with recurrent abdominal pain.

Diagnosis is established by—(a) endoscopic *mucosal biopsy* from ulcer site using *rapid urease test*, or (b) *breath test*, to demonstrate urease production by increased excretion of radio-labeled CO_2 after ingestion of $C^{14/13}$ labelled urea.

Treatment is recommended only in symptomatic cases with triple-drug therapy for 2 weeks to eradicate infection. It includes an oral combination of clarithromycin (250–500 mg) or amoxicillin (500–750 mg) *with* metronidazole (250–500 mg) *and* PPI, e.g. omeprazole (20–30 mg), using lower range of doses mentioned against each drug for children 15–24 kg and higher range for those >25 kg.

Bezoars, i.e. an *accumulation of exogenous matter in stomach or intestine*, are more common in mentally challenged children and in females. Depending on type of matter, bezoars are called *trichobezoars* (hair), *phytobezoar*

Fig. 14.11: **Trichobezoar (plain X-ray).**

Fig. 14.12A: **Duodenal atresia (double-bubble sign).**

(plant/animal material), *lactobezoar* (casein/calcium of top milk), etc.

These cases usually present in second decade with recurrent abdominal pain, vomiting, palpable lump in left hypochondrium and sub-acute obstruction. Failure to thrive is common.

Abdominal X-ray may show bezoars in plain or barium-contrast films **(Fig. 14.11)**, though endoscopy is useful for diagnosis as well as removal. Lactobezoars usually resolve spontaneously after 24–48 hours.

14.9 INTESTINAL MALFORMATIONS

Congenital malformations of lower gastrointestinal tract may be divided into three categories—(a) *small bowel malformations*, e.g. atresia, malrotation, etc., (b) *colorectal malformations*, e.g. Hirschsprung disease or anorectal anomalies, and (c) *abdominal wall defects* with gut herniation.

14.9.1 SMALL BOWEL MALFORMATIONS

Small bowel malformations are leading causes of intestinal obstruction in newborns and young infants, though many of them present in later life or remain asymptomatic throughout the life.

Duodenal atresia: Duodenal atresia is rare (~1:10,000 live births) but important defect, characterised by *developmental failure of the recanalization of duodenal lumen* after solid phase of intestinal development, producing stenosis, atresia or a mucosal web in the duodenal lumen, usually at the site of papilla of vater.

Chromosomal abnormalities, e.g. Down syndrome are present in ~25% cases, while >30% have other gut malformations, e.g. malrotation, esophageal atresia, anorectal anomalies, etc. or congenital heart diseases. Half of these cases are preterms. Polyhydramnios is present in >50% cases, due to failure of the absorption of amniotic fluid.

Clinically, these cases present within 24 hours of birth with—(a) bilious vomiting/gastric aspirate *without* abdominal distension, and (b) visible peristaltic waves in upper abdomen. Jaundice is present in 1/3rd cases due to blockade of ampula of Vater.

Diagnosis rests on X-ray abdomen showing pathognomonic *double-bubble sign*, i.e. one air-fluid level in the distended stomach and another in the first part of distended duodenum. Rest of the gut has no air shadows **(Fig. 14.12A)**.

Prenatal diagnosis is possible on USG, while postnatal USG is necessary before surgery to exclude other malformations or causes of duodenal obstruction, e.g. annular pancreas, peritoneal bands, volvulus, etc.

Management: Immediate *duodenoduodenostomy or duodenojejunostomy* is necessary in all cases, after *preoperative stabilization* with nasogastric decompensation, fluid/electrolyte correction, etc. and *exclusion of other malformations*. Postoperative oral feeds may be started after ~1 week, after disappearance of duodenal ileus.

Jejunoileal atresia: Jejunoileal atresia is twice more common than duodenal atresia and have been attributed to intrauterine infections or vascular accidents.

These defects are of four types—*type I*, with an intraluminal diaphragm; *type II*, with a solid cord between proximal and distal segments; *type III,* with blind loops on both ends of bowel with mesenteric defects; and *type IV,* with multiple atretic segments. Type III is most common (35%).

Clinically, these defects invariably present within 24–48 hours with meconium ileus and acute intestinal

Fig. 14.12B: **Jejuno-ileal atresia (Triple bubble sign).**

obstruction. Polyhydramnios is present in ~ 25% cases. **Diagnosis** rests on plain X-ray abdomen, showing three fluid levels (*Triple-bubble sign*, **Fig. 14.12B)**, meconium ileus (*ground-glass appearance* in right lower quadrant) and/or evidence of perforation, i.e. gas under diaphragm. Presence of peritoneal calcifications suggests meconium peritonitis.

Treatment involves immediate surgical exploration with resection-anastomosis or proximal jejuno/ileostomy, after pre-operative stabilization.

Malrotation (Volvulus): Most of the mid-gut in early fetal life lies outside the abdomen cavity, but re-enters later with a rotation around the axis of superior mesenteric artery, which allows placement and fixation of intestinal structures at normal locations. Malrotation or non-rotation leads to abnormal location of these structures, commonest defect being the failure of the cecum to move in right lower quadrant.

Volvulus refers to an acute or recurrent symptomatic complication of malrotation, which need immediate intervention.

Clinically, most cases of malrotation (60–80%) present in infancy as volvulus with acute intestinal obstruction, while rest may present as chronic obstruction with recurrent abdominal pain and vomiting. However, ~25–50% cases with mild defects remain asymptomatic or present beyond childhood.

Diagnosis usually depends on USG or barium contrast studies. Plain X-rays are often non-specific.

Treatment: Surgical intervention is indicated in all diagnosed cases irrespective of age, usually along with incidental appendectomy.

Meckel's diverticulum: Meckel's diverticulum is a 3–6 cm out-pouch of the ileum along the anti-mesentric border, ~50–75 cm away from ileocecal junction. It represents *attenuated omphalomesenteric duct, which* connects the yolk sac with developing embryo before development of placenta.

Pathologically, it is a true diverticulum with all intestinal layers, lined by the heterotopic gastric mucosa. Pancreatic tissue or jejunal/colonic mucosa may also be present.

Incidence: Meckel's diverticulum is the *commonest* congenital malformation of gut, present in 1.5–2.0% of normal population, more common in males (2:1). It may also be associated with other gut malformations, e.g. esophageal atresia, anorectal anomalies, etc. *or* Crohn disease.

Clinically most cases are asymptomatic. Symptomatic cases usually present in first two years of life with complications, e.g. (a) intermittent painless rectal bleeding, (b) acute intussusception with diverticula as its lead point, or (c) acute abdominal pain due to *diverticulitis* or impacted roundworms in diverticula. Rarely, tumors, e.g. carcinoid tumor may originate from diverticula in late life.

Diagnosis: A radionucleotide scan with Tc^{99m} to delineate gastric mucosa is the best diagnostic method to detect Meckel's diverticulum with >85% sensitivity and specificity (*Meckel's scan*). Sensitivity may be further enhanced with prior administration of cimetidine, pentagastrin or glucagon.

Other investigations, e.g. rectosigmoidoscopy may be necessary to exclude other causes of rectal bleeding.

Management: Open or laparoscopic *wedge resection of the diverticulum or segmental resection of the ileum bearing the diverticulum* is indicated in all symptomatic cases after pre-operative stabilization. In asymptomatic, incidentally detected diverticula, resection is advisable in cases with—(a) diverticular length >2 cm, (b) younger age <40 years and (c) presence of heterotopic mucosa.

Peutz-Jeghers syndrome is a rare autosomal dominant disorder, characterized by multiple gastric and intestinal polyps with perioral and oral hyperpigmentation and presenting with recurrent abdominal cramps, intussusception and occasional gastrointestinal bleeding.

14.9.2 HIRSCHSPRUNG'S DISEASE

Hirschsprung's disease (*congenital megacolon*) is characterized by the *absence of ganglionic cells* in a variable length of colon, proximal to anorectal junction. Consequently, the involved segment fails to propel normal peristalsis, leading to physiological obstruction.

Aganglionic segment is usually limited to rectosigmoid junction, i.e. classic short-segment disease (75%), but may also involve a longer segment (10%), full-length colon (10%) or rarely, even a part of ileum (<3%). However, in some cases of ultra-short-segment (USS) disease, only internal sphincter is involved.

Incidence: Hirschsprung disease is seen in ~1:5000 live births, more common in males (4:1) and fullterms. It is uncommon in preterms. *Recurrence risk is ~6%.*

Etiopathogenesis: Normally, the neuroenteric cells in embryonic neural crest migrate in fetal life to form muscular *(Auerbach's)* and submucous *(Meissner's)* nerve plexi of bowel walls. Hirschsprung's disease is a multifactorial disorder due to failure of this migration, which normally occurs in cephalocaudal manner from proximal to distal bowel.

Genetic defects may involve multiple genes which encode proteins involved in RET signaling pathway *(RET, GDNF,* and *NTN) or* endothelin type B receptor pathway *(EDNRB, EDN3,* and *EVE-1).*

Physiological obstruction due to impaired peristaltic movements in aganglionic segment leads to gradual stasis and dilatation in proximal colon with risk of secondary infections, i.e. enterocolitis.

Clinically, severe disease may present at birth with delayed passage of meconium though most cases manifest beyond 2nd week of life with—(a) chronic constipation, (b) pellet or ribbon-like stools, (c) abdominal distension, and (d) intermittent diarrhea or enterocolitis. Gradually, these children develop failure to thrive and other signs of malabsorption, e.g. edema and anemia.

Per-rectal examination is nearly diagnostic with—*(i) normal anal tone, (ii) empty rectum despite constipation and (iii) explosive discharge of foul-smelling fecal matter and gases on withdrawal of finger*. Fecoliths may be palpable on abdominal examination.

Diagnosis: While per-rectal findings are highly suggestive, following investigations are necessary to confirm the diagnosis and assess the extent of bowel involvement before surgery:

- *Barium enema* revealing—(i) dilated proximal colon, (ii) constricted distal colon, (iii) a funnel/cone shaped zone of transition between them, and (iv) incomplete evacuation of barium even after 24 hours, in late X-ray films **(Fig. 14.13)**. However, a normal barium enema does not exclude Hirschsprung disease.
- *Anorectal manometry* is highly reliable (90%) but technically difficult procedure in newborns, which reveals absence of normal relaxation in internal sphincter, after distension of rectum.
- *Rectal biopsy* is the *gold standard* for diagnosis, which may be done pre-operatively (submucosal suction biopsy, at least 2 cm above the dentate line) or during surgery (full thickness biopsy, to assess extent of involvement). Histopathologically, it reveals—(i) absence of ganglionic cells, (ii) presence of hypertrophied nerve bundles and (iii) elevated *Acetyl cholinesterase* levels on special staining. Rectal biopsy may be false normal in USS disease.

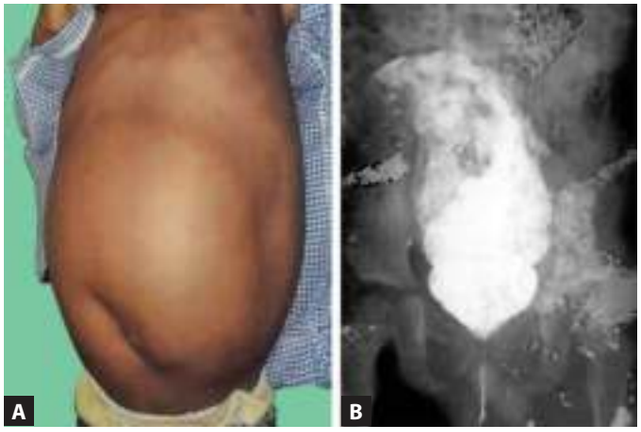

Fig. 14.13: Hirschsprung's disease: (A) Abdominal distension; (B) Barium enema.

TABLE 14.11: Congenital megacolon vs functional constipation

	Cong. megacolon	*Functional constipation*
Clinical		
Age of onset	<1 month	>1 year
Stools	Ribbons/pellets	Normal/hard
Diarrhea	Intermittent	None
Encopresis	Rare	Common
Failure to thrive	Yes	No
Abd. distension	Yes	Minimal
Per-rectal examination		
Anal tone	Tight	Patulous
Rectum	Empty	Fecoliths
Post-PR evacuation	Immediate	Late or none
Investigations		
Ba. enema	Transition zone	No TZ
Internal sphincter*	Tight	Relax
Rectal biopsy	Absent ganglions	Normal

*on anorectal manometry, **PR:** Per-rectal examination; **TZ:** Transition zone

D/D of Hirschsprung's disease includes other causes of constipation in newborns and young infants (Ch 14.4.4), specially—(a) functional or habitual constipation **(Table 14.11)**, (b) hypothyroidism, and (c) anorectal malformations.

Management: Definitive management is essentially surgical, after pre-operative stabilization with-(a) correction of fluid and electrolyte disturbances, (b) treatment of acute enterocolitis with appropriate antibiotics, and (c) provision for adequate nutrition.

Surgical options depend on the length of aganglionic segment and general condition of newborn. Direct corrective surgery may be performed in cases with small lesions in good health, though most cases require

a *two-stage procedure*—immediate temporary *colostomy followed by definitive repair* after 6–12 months. Efforts are made to preserve anal canal and sphincter mechanisms to achieve continence. Various corrective procedures are used depending on the severity of lesion and experience of surgeons, including:

- *Duhamel's pull-through operation*, i.e. transabdominal or laparoscopic construction of a new rectum, by bringing down normally innervated colon behind the aganglionic segment.
- *Boley's endorectal pull-through operation*, i.e. stripping the mucosa of aganglionic segment and bringing down the normally innervated proximal colon through the residual muscular cuff.
- *Classic Swenson's procedure*, i.e. excision of involved segment with end-to-end anastamosis between proximal bowel and rectum, 1–2 cm above the dentate line, is no longer preferred.
- USS disease needs only the excision of a strip of rectal muscle, including internal anal sphincter.
- Hirschsprung's disease involving whole length of colon needs ileal-anal anastamosis.

Prognosis: With timely management, prognosis is usually excellent, though complications like- (a) fecal incontinence (b) leaks/stenosis at anastamotic site (c) perineal abscesses/fistulas and (d) colostomy problems, e.g. enterocolitis are common.

14.9.3 ANORECTAL MALFORMATIONS

Anorectal malformations (ARMs) include a group of heterogeneous developmental defects involving rectum and anal canal with absence, stenosis or ectopic opening of anus and/or fistulous connections with urogenital tract. These defects are present in ~1/1000 live births

Embryogenesis: Rectum and anal canal develop from common cloaca along with lower urogenital tract, which separate with each other by formation of a urogenital septum by 7–8th week. ARMs represent defects in the formation of urogenital septum or failure of its fusion with cloacal membrane.

Continence in these cases depends on involvement of: (a) *neurogenic components*, i.e. sacral outflow from $S_{2\text{-}4}$, (b) *myogenic components*, i.e. levator ani and external sphincters, and (c) *sensory perception* of pain, touch, temperature and propioception.

Classification: ARMs are best classified according to their relationship with the main muscle of continence, i.e. levator ani, (which is present as a sling around the rectum and controls the flow of feces along with external sphincter) as *high, intermediate* or *low* defects **(Table 14.12)**. *Recto-vestibular and recto-urethral fistulas are commonest ARMs in females and males respectively.*

Clinical spectrum: While most ARMs, e.g. imperforate anus are diagnosed at birth during routine orificial examination, many are missed in first 24–48 hours and present with-(a) failure to pass meconium, (b) passage of meconium from abnormal sites, e.g. urine or vagina, (c) gradual abdominal distension with signs of intestinal obstruction. Rarely, some malformations, e.g. anal stenosis, presents in older children with chronic constipation and fecaloma.

TABLE 14.12: Classification of anorectal malformations

- **Supralevator (HIGH) anomalies**
  - Anorectal agenesis
  - Persistent Cloaca (in females)*
  - Rectal atresia (normal anal canal/opening)
- **Infralevator (LOW) anomalies**
  - Ano-rectal membrane (imperforate anus)
  - Ectopic anus (perineal fistulas)
  - Anal stenosis
  - Ano-vulval fistula
  - Recto-vaginal fistula
- **Translevator (intermediate) anomalies**
  - Anal agenesis
  - Recto-vestibular fistula (commonest ARM in females)
  - Recto-urethral fistula (commonest ARM in males)
  - Recto-vesical fistula

*Rectum, vagina and urinary tract fuse to form a common channel, opening as a single orifice behind the clitoris.

Perineal examination may help to identify the type of defect and localize ectopic anal opening. While perineum is usually flat without median raphe and anal dimple in high types, presence of median raphe and anal dimple indicate low or intermediate defects with relatively spared sphincteric mechanisms and better post-operative chances for continence.

High ARMs are frequently associated with sacrospinal deformities (>25%), urogenital malformations (>50%) and other gut malformations, which should be excluded before surgery.

Diagnosis aims to-(a) identify the precise anatomical defect before surgery and (b) search for associated urological, spinal and neurological problems. Important investigations include:

- *Ultrasonography* is the preferred choice to differentiate between high and low ARMs as well as to identify associated urological abnormalities. A distance from rectal pouch to perineum <10 mm indicates low imperforate anus, while a distance of >15 mm suggests high defects. Spinal canal may also be scanned by USG for a latent tethered cord during first 3 months of life, though MRI is more reliable.
- *Invertograms* have been conventionally used for diagnosis of ARMs, though gradually being replaced with USG. Invertogram should be performed at least 12 hours after birth to allow intestinal gases to reach till most distal part of rectal pouch. Baby is held upside down (inverted) or knee-chest position for 3 minutes, before X-ray exposure. Location of gas shadow in the

Fig. 14.14: **Anorectal malformations (Invertogram).**

rectal pouch is then compared with pubococcygeal and puboischial lines, (i.e. lines representing levator ani muscle) to differentiate between low or high ARMs. When the rectal gas pouch in invertogram is >1 cm away from skin, patient probably has high/intermediate defect and needs initial colostomy before corrective surgery **(Fig. 14.14)**.

Treatment: The choice of surgical procedure depends on the type of defect, general condition of patient and associated urological or neurospinal defects.

Low malformations like simple imperforate anus may be managed with single-step *Anoplasty* with *transpositioning for fistulous tracts* in neonatal period, followed by repeated anal dilatations, till the normal anal size is achieved.

High/intermediate defects need a two-step surgery, involving preliminary colostomy followed by definite corrective repair after 6–12 months. Corrective surgery involves a pull-through procedure to bring the colon below the level of levator ani sling (for continence), to open it at expected anal site and to close the fistulous tracts.

Prognosis depends on the type of defect and co-existing defects. Success rate for fecal continence is excellent in low-defects (>80–90%) and moderate (50–60%) in intermediate defects. However, children with persistent cloaca of >3 cm length or recto-vesical fistula rarely achieve adequate continence. Surgical complications include anorectal stenosis, prolapse and recurrence of fistula.

14.9.4 ABDOMINAL WALL DEFECTS

While not the intestinal malformations in true sense, abdominal wall defects are important causes of the herniation of intestines or other abdominal viscera in newborn or young infants. Some important abdominal wall defects are as follows:

Umbilical hernia due to incomplete closure of the fascia of umbilical ring, presents with herniated omentum or bowel, *covered with skin.* Umbilical hernia of <1.5 cm usually close spontaneously by 4 years of age and complications, e.g. intestinal incarceration are rare.

Surgical closure is advisable if defect exceeds 1.5 cm at 2 years of age. Manual reduction with strapping over the ring does not accelerate closure of defect and is no longer advised.

Omphalocele, i.e. herniation of abdominal viscera through umbilical and supraumbilical portions of abdominal wall at birth, denotes incomplete migration of bowel from the umbilical coelom. Herniated organs are *covered with a peritoneal sac*, which may rupture *in utero* or at birth. Associated anomalies are common, e.g. gut malformations, CHDs and Beckwith-Wiedemann syndrome. Primary closure is possible for small defects, while larger defects need two-stage repair.

Gastroschisis is the herniation of the variable length of intestines or other abdominal viscera, *without a covering sac*, through a para-umbilical defect. Eviscerated organs may be covered by a gelatinous matrix of greenish material at birth. Most of these cases are preterm and ~20% have other congenital anomalies. Gastroschisis is a surgical emergency, though single-stage repair is rarely possible.

Inguinal hernia denotes *protrusion of a part of abdominal viscera, usually the intestine through inguinal canal.*

Incidence of inguinal hernia in children is estimated to be ~1–3% live births, more common in males (4–8:1) and preterms. About 99% of inguinal hernias are indirect and more common on right side (60%). Direct inguinal hernia or femoral hernia is rare in children.

Etiologically, *patency of processus vaginalis* is the principle defect in inguinal hernia, seen in ~80–90% at birth and ~50% at 1 year. Calcitonin-gene related polypeptide (CGRP) plays an important role in its closure. Other contributing factors for hernia include: (a) chronic cough, (b) connective tissue disorders, e.g. Ehlers-Danlos syndrome, (c) undescended testis, and (d) ascites.

Clinically these cases present with inguinal swelling that increases on crying or straining. *Silk glove sign*, i.e. silky feeling of processus vaginalis on rubbing over the spermatic cord may be present. Hydrocele, due to patent processus vaginalis, usually co-exists as scrotal swelling.

Complications of hernia include: (a) incarceration, (b) obstruction, (c) gangrene, and (d) testicular damage.

Management is essentially surgical with open or laparoscopic *herniotomy and closure of hydrocele sac.* As ~10–15% cases may later develop contralateral hernia, routine exploration on other side for patent processus vaginalis is advisable in boys <1 year and in all girls with left-sided hernia.

14.10 ACUTE DIARRHEA

Diarrheal disorders are second commonest cause of morbidity and mortality in preschool children, after acute respiratory infections. Since normal frequency of stools varies significantly in children, diarrhea is defined as 'a *change in the usual frequency or consistency of stools'*. Presence of blood or mucus in stools denotes *dysentery* (Ch 10.8).

Diarrheal disorders may be classified as:

- *Acute diarrhea*, lasting for <14 days; discussed in this chapter
- *Persistent diarrhea,* i.e. continuation of an acute diarrheal episode for >14 days (Ch 14.11)
- *Chronic diarrhea* of >14 days duration, due to disorders of malabsorption (Ch 14.12).

Incidence: Usually underreported, acute diarrhea accounts for ~30% of hospital admissions and ~15% of deaths in under-5 children. NFHS-5 (2019–21) reveals that ~7% under-five children in India had diarrhea during preceding two weeks of survey visit.

Epidemiology: Acute diarrhea is most common in 6 months-3 years age-group, specially in children with following ***risk factors***—(a) top feeding, (b) contaminated water supply, (c) low socioeconomic status, (d) poor sanitation and excreta disposal, (e) unhygienic food habits, (f) malnutrition, and (g) vitamin A deficiency.

Diarrhea and malnutrition have a cause-effect relationship. While diarrhea is common in malnourished children due to—(a) gut mucosal atrophy, and (b) colonic overgrowth of bacteria due to impaired immune defence; each diarrheal episode worsens the nutritional status due to—(a) anorexia, (b) poor absorption, (c) increased nutritional requirements and sometimes, (d) misconceived starvation of child due to fear of increasing diarrhea after feeding.

Etiology: More than 90% of infantile diarrhea are infective in origin **(Table 14.13)**.

Rotavirus is the commonest cause of acute diarrhea in infants and toddlers, responsible for >50% and ~25–30% episodes, respectively. Seven serotypes are known to cause human disease, the commonest in India being G1P8, responsible for ~60% cases.

Infection is acquired feco-orally, usually in 3–24 months age-group and during winter or spring season. Over half of the cases are asymptomatic. Symptomatic infection is self-limiting within 3–5 days but persistent diarrhea due to secondary lactose intolerance is not uncommon.

Bacterial diarrhea: *E. coli,* with its four sub-types, i.e. enterotoxigenic (ETEC), enteropathogenic (EPEC), enteroadherent (EAEC) and enteroinvasive (EIEC), is the second commonest (25%) cause of diarrhea in Indian children. Of these, ETEC is most common, with serotype

TABLE 14.13: Common causes of acute diarrhea

- **Infective diarrhea**
  - *Viral:*
    Rotavirus (25–50%)
    Others: Astroviruses, enteroviruses
  - *Bacterial:*
    E. coli, (25%)
    V. cholerae (5–10%)
    C. jejuni (5–10%)
    Shigella/Salmonella (5–10%)
  - *Protozoal:* Giardiasis, amebiasis
  - *Parasitic:* Intestinal helminthes
  - *Opportunistic:* Candida, spore-forming protozoa*
- **Parenteral diarrhea:** Non-GIT infections, e.g. ARI, UTI, otitis media
- **Non-infective diarrhea**
  - *Drug-induced:* Antibiotics, laxatives, iron
  - *Toxins:* Food poisoning**, heavy metals
  - Food allergy
  - *Others:* Overfeeding, psychogenic diarrhea

*Cryptosporidium, isospora bacilli, cyclospora, microsporidia
**Due to pre-formed toxins, e.g. *Staph. aureus, C. difficile*

E-0159 emerging as an important cause of cholera-like outbreaks. EPEC is more common in urban children or as Traveller's diarrhea, while EAEC or EIEC usually present as bacillary dysentery.

Other bacterial pathogens, e.g. *V.cholerae, Shigella and Salmonella infections* accounts for 10–15% cases. *Camplyobactor jejuni*-a zoonotic infection, transmitted by excreta-contaminated food/water, is an emerging cause of acute infantile diarrhea.

Protozoal diarrhea: *Amoebiasis* is relatively less common in children than *Giardiasis*—a leading cause of diarrhea in malnourished children. Spore-forming protozoa, e.g. *cryptosporidium, isospora, cyclospora* and *microsporidia* are predominant causes of recurrent diarrhea in immunocompromised children, though small outbreaks of mild diarrhea are common even in normal children.

Parenteral diarrhea denotes increased gut motility in extraintestinal infections, e.g. otitis media, ARI or UTI, which usually disappears spontaneously or after treatment of primary infections.

Food poisoning is an important cause of acute diarrhea, when multiple children and/or adults are affected simultaneously after common food ingestion.

Pathogenesis-wise, diarrhea may be broadly divided into following categories:

- ***Secretory diarrhea*** by exotoxin-producing pathogens, e.g. cholera or ETEC, due to stimulated production of adenylyl cyclases and cyclic AMP/GMP leading to increased ATP activity and active secretion of sodium and water in gut lumen.
- ***Osmotic diarrhea***, i.e. passive outflow of water, due to increased osmotic load in gut, e.g. in lactose intolerance.

- ***Invasive diarrhea*** (dysentery) due to actual mucosal invasion, e.g. EIEC, EAEC and Shigella infections or *adhesion of pathogens* to mucosal cell walls without destruction, e.g. EPEC.
- ***Hypermotility diarrhea*****,** due to parenteral infections or non-infective causes, e.g. drugs, overfeeding, psychogenic causes, etc.

Pathophysiology: *Dehydration and electrolyte disturbances are most important complications of diarrhea,* due to excess loss of water and electrolytes (mainly sodium) in stools. While initial losses are mainly from extracellular fluid compartment (ECF), consequent changes in plasma osmolality lead to redistribution of body fluids, as follows:

- When water and sodium loss is nearly proportional as in osmotic diarrhea, serum osmolality is maintained, leading to *isotonic dehydration* (50% of total diarrhea).
- When sodium loss is disproportionately more than the water loss as in secretory diarrhea, serum osmolality falls leading to *hypotonic dehydration* (30–40%). In these cases, extracellular hypotonicity moves water from ECF to ICF, accentuating ECF dehydration and hypovolemia. Consequently, signs of dehydration are relatively more marked than the actual fluid loss in hypotonic dehydration.
- Rarely, and specially when dehydration is erroneously treated with concentrated ORS or hypertonic parenteral fluids, serum osmolality rises to cause *hypertonic dehydration* (5%). In these cases, extracellular hypertonicity withdraws water from ICF to ECF, leading to cellular dehydration. Signs of dehydration are relatively less prominent than actual fluid deficit in hypertonic dehydration.

Severe ECF depletion and hypovolemia leads to compensatory responses, e.g. peripheral vasoconstriction (cold skin, dry mucosa), hyperdynamic circulation (weak-thready pulse), oliguria, and finally, the hypotension/shock. As considerable amount of potassium and bicarbonates (intestinal pH is alkaline) is also lost in stools, *hypokalemia* and *acidosis* is common in diarrhea-induced dehydration.

Diagnostic assessment of a child with diarrhea may be divided into: (a) clinical assessment of the severity of dehydration, (b) clinical assessment of the etiology, and (c) relevant laboratory investigations.

- **Assessment of dehydration:** Important indicators of the severity of dehydration (as mild, moderate) or severe are given in **Table 14.14**. However this assessment may be unreliable in:
  - *Malnourished children,* due to overestimation of turgor loss in wasted marasmus and underestimation in edematous kwashiorkor.
  - *Chubby children*, due to underestimation of turgor loss. Urine output is the most reliable indicator of dehydration in malnourished or obese children.

TABLE 14.14: Assessment of severity of dehydration

Feature	*Mild*	*Moderate*	*Severe*
Behavior	Alert	Drowsy*	Stupor/coma
Thirst	Thirsty	Marked	Absent
Eyeballs	Normal	Sunken	Sunken
Tears	Present	Absent	Absent
Tongue	Dry	Dry	Parchmenty
Skin turgor	Normal	Lost*	Lost
Pulse	Normal	Rapid	Thready
Respiration	Normal	Rapid	Acidotic
BP	Normal	Normal	Hypotension
Urine output	Normal	Oliguria	Anuria
*Weight loss***	3–5%	6–10%	9–15%

*Irritability and doughy skin in hypernatremic dehydration.
**Higher % of wt loss in infants.

  - *Hypernatremic dehydration,* due to relative preservance of ECF that leads to underestimation of dehydration. Presence of hyperirritability and doughy skin are strong indicators in these cases.
  - *Hyponatremic children* are at risk of developing early circulatory failure and shock despite lesser fluid and weight loss due to water movement from ECF to ICF.

  According to IMNCI guidelines, dehydration in children with diarrhea is classified as (a) severe dehydration, (b) some dehydration, and (c) no dehydration, based on four indicators—(1) general condition; (2) eye balls, (3) ability to drink water and (4) skin turgor **(Table 29.2)**.

  "*Severe dehydration*" is indicated by presence of *any two* of the following four signs: (a) lethargy/unconsciousness, (b) sunken eyes, (c) inability to drink, and (d) very low skin turgor; While "*Some dehydration*" is indicated by *any two* of following four signs: (a) restlessness and irritability, (b) sunken eyes, and (c) thirsty, drinks eagerly, and (d) low skin turgor. Absence of enough signs suggests "*no dehydration*".
- **Clinical assessment of etiology:** Viral, bacterial and protozoal diarrhea may be distinguished up to certain extent on the basis of age, nutritional and immune status, seasonal trends, clinical features and appearance of stools **(Table 14.15)**. Some important indicators are as follows:
  - Large-watery diarrhea in apparently healthy infant or toddler suggests rotavirus infection. Perianal excoriation is common.
  - Rice-water stools indicate cholera and entero-toxigenic *E.coli* infection.
  - Presence of blood/mucus in stools with high fever, toxic look and cramps suggest bacterial etiology.
  - Watery, foul-smelling stools with/without blood, in school-going children may be amebic in origin.
  - Watery or bulky diarrhea with fat globules, specially in malnourished children suggest giardiasis.
- **Laboratory evaluation** in diarrhea includes:

TABLE 14.15: D/D viral, bacterial and protozoal diarrhea

	Viral	*Bacteria*	*Protozoal*
Epidemiology			
Common Age	Infants	Pre-school	School-age
Nutrition	Normal	PEM	N/PEM
Immune status	Normal	N/↓	N/↓
Season	Winter	Monsoons	Monsoons
Clinical			
Onset	Acute	Sub-acute	Sub-acute
Fever	+/–	++	–
Toxemia	–	++	–
Vomiting	++	+/–	–
Dehydration	++	+++	+
P'anal redness	+++	+	+/–
Stool findings			
Volume	Large	Large	Variable
Consistency	Frothy	Curdy	Bulky
Odor	Odorless	+/–	++
Blood/mucus	Absent	+	+/–
Fat globules	–/+	–/+	++
Microscopy			
Pus cells	–/+	>10/hpf	+/–
Cysts	–	–	+
Common cause	Rotavirus	ETEC	Giardia

ETEC: Enterotoxigenic *E.coli*, **EH:** *Entamoeba histolytica*

- ***Stool examination,*** specially for pH, reducing sugar, fecal leukocyte count, fat globules, parasitic cysts/ova. Hanging-drop preparation is essential in rice-water stools to exclude cholera.
- ***Stool cultures*** are of limited value due to poor specificity, but indicated in—(a) suspected cholera, (b) critically sick children to exclude nosocomial infection, and (c) immunocompromised states to exclude opportunistic pathogens.
- ***Specific investigations:*** Virological diagnosis of rotavirus by electron microscopy or ELISA test is possible, but rarely available. ELISA tests to detect ETEC or vibrio toxins are also available.
- ***Supportive investigations*** including serum electrolytes, blood gas analysis and renal functions, e.g., blood urea or serum creatinine, are necessary in severe dehydration.

Management of acute diarrhea includes—(I) fluid replacement therapy, (II) nutritional management, (III) specific antidiarrheal agents, and (IV) treatment of associated infections and other complications.

I. Fluid replacement therapy is the cornerstone of management in acute diarrhea, to prevent and correct dehydration. The mode of fluid replacement (oral *vs.* parenteral) depends on severity of dehydration and child's willingness or tolerance (vomiting) for oral fluids.

WHO guidelines (2005) regarding fluid therapy in childhood diarrhea **(Fig. 14.15)**, are based on three options:

- ***Plan A*** to prevent dehydration in children with "*No dehydration*" providing oral rehydration solution (ORS) at home as follows—50–100 ml after each stool in children < 2 years, 100–200 ml after each stool in 2–10 years old and ad libitum in older children.
- ***Plan B***, i.e. supervised ORS administration in the hospital for children with *some dehydration*. The amount of the ORS to be given during first 4 hours depends on the age of the child, as stated in **Fig. 14.15**.
- ***Plan C***, i.e. parenteral rehydration in cases with severe dehydration (see Parenteral fuild therapy below).

Frequent re-evaluation and necessary modifications in fluid therapy is essential in all cases. Some important aspects of oral and parenteral fluid therapy are discussed here:

Oral rehydration therapy is the preferred mode of fluid replacement in diarrhea for—(a) prevention of dehydration, and (b) correction of mild to moderate dehydration. It may be safely used in all cases of diarrhea except those with—(a) paralytic ileus (when oral feeding needs to be withheld), and (b) altered sensorium (risk of aspiration). Children with vomiting may be given oral fluids after anti-emetic therapy.

Oral rehydration solution (ORS) is one of the most important medical advance in last century, which has reduced the diarrhea-related mortality by >80%.

Principle of ORS therapy in diarrhea is based on following facts:

- Large amount of fluids are lost in diarrhea, which needs to be replenished with fluids.
- Substantial amount of sodium and other electrolytes are also lost in diarrhea. As sodium is the principle determinant of ECF osmolality, its presence is a must in any ORS.
- Water absorption in gut is largely passive, dependent on active sodium absorption.
- Absorption of glucose and amino acids are carrier-dependent and remain largely intact in most cases of diarrhea.
- Carrier mechanisms for sodium absorption are interlinked with glucose/amino acid absorption and co-administration of glucose or amino acids in ORS facilitates sodium/water absorption.
- Since excess intake of glucose may cause osmotic diarrhea, 1:1 molar ratio of glucose and sodium concentration in ORS is most appropriate to maximize sodium reabsorption with minimal osmotic load.
- As potassium and bicarbonates losses are also common in GIT fluid loss, ORS should also contain minimum required concentration of these electrolytes.

WHO-ORS contains 75 mEq/L of sodium with osmolality of 245 mEq/L, in composition as given in **Table 14.16**. It

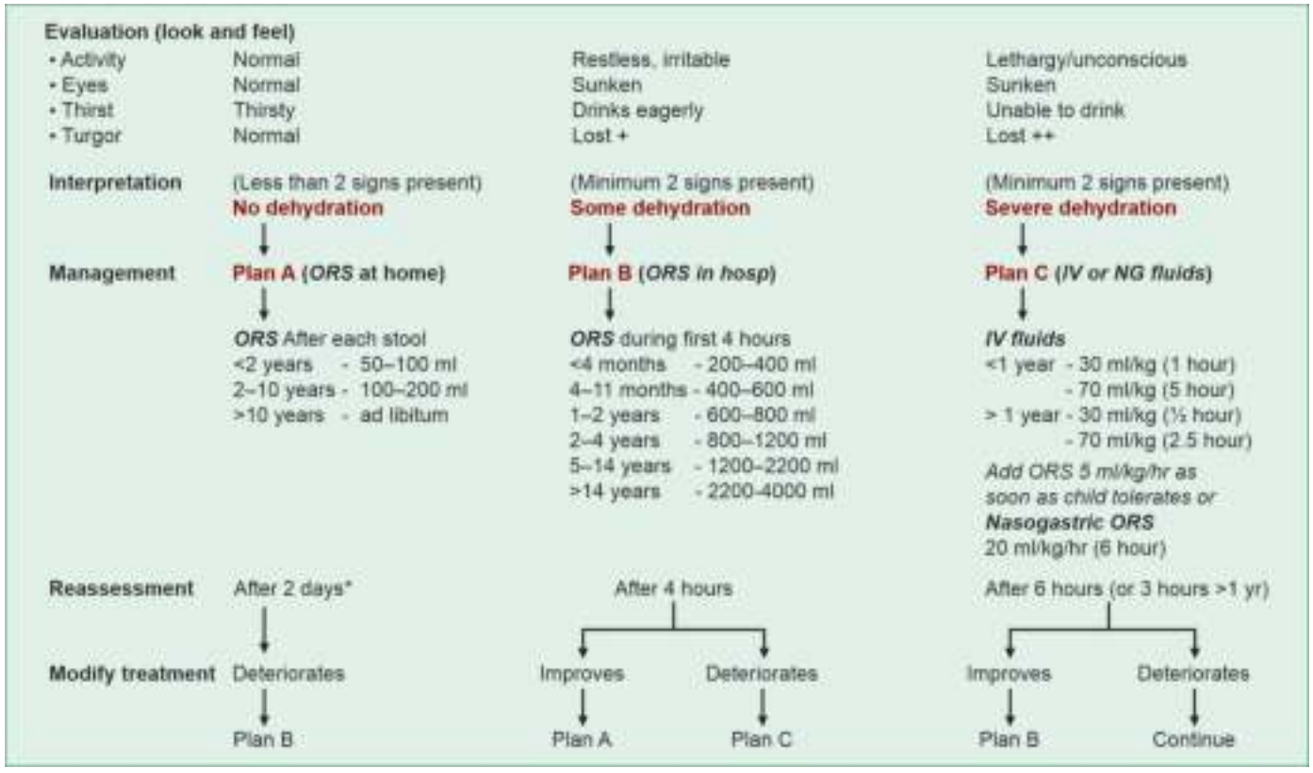

Fig. 14.15: WHO/National task force guidelines for management of diarrhea in children.

*Teach mother about danger signs or dehydration and ask to report immediately

**Give 1 packet of ORS in plan A and 2 packets in plan B for home use, before sending home

Source: WHO (2005): The treatment of diarrhea: A manual for physicians and other senior health workers.

is supplied free of charge by the government at health centers and is also available commercially.

Preparation and storage: WHO-ORS must be prepared hygienically, mixing one packet of ORS in one liter (~5 glass) of potable, clean water. Once prepared, it should be stored in a clean container and may be used till 24 hours. Pre-packed ORS has a shelf-life of 2 years. Smaller packs of ORS, to be dissolved in 200 ml are also available commercially, as also ready-to-use solutions.

Dosage and administration: It may be fed with spoon or a large cup *ad libitum* (as much as desired) for prevention of diarrhea, with minimum quantities as stated in **Figure 14.15** for Plan A and B in children with dehydration.

TABLE 14.16: Composition of WHO-ORS

Constituents	*Weight (gm/dl)*	*Electrolytes*	*(mmol/L)*
Sodium chloride	2.6	Na^+	75
Potassium chloride	1.5	K^+	20
Tri-sodium citrate	2.9	Citrate	10
Glucose	13.5	Cl^-	65
Water	1000	Glucose	75
Osmolality			245

Side-effects: WHO-ORS is extremely safe, except potential risk of hypernatremia due to use of wrongly concentrated ORS. In addition, mothers may erroneously perceive ORS as replacement for regular feeding, which should be continued in all cases.

Modified ORS: Various other ORS preparations with different composition have been developed to maximize sodium/water absorption or reduce the risk of hypernatremia/osmotic diarrhea in special situations. Some are as follows:

- ***Resomal*** (*Re*hydration *so*lution for *Mal*nourished children) with 45 mEq/L of sodium, is preferred in malnourished children due to higher risk of hypernatremia. Not commercially available in India, it may be prepared by diluting one pack of WHO-ORS in 2 liters of water and adding 50 gm of sucrose as well as 40 ml of mineral-mix solution (Ch 6.1).
- ***Enriched or super ORS*** is prepared by—(i) addition of certain amino acids, e.g. glycine, L-alanine or glutamine in standard ORS; *or* (ii) replacement of glucose with a starch preparation, e.g. pre-cooked or puffed rice powder (~ 50 gm/L). While amino acids enhance the sodium co-transport and reabsorption (independent of glucose-based transport), starch-based preparations reduce the risk of osmotic diarrhea

by slower release of glucose. While these variants might be marginally superior in cholera, no significant benefits over WHO-ORS have been observed in non-choleric diarrhea and tend to affect the palatability or cost of preparation.

- ***ORS in very young infants:*** Although WHO-ORS may be safely used in all children, a diluted preparation (1 pack in 1.5 liter of water) may be used in very young infants <2 months, to avoid osmotic load. However, breastfeeding is usually adequate in these cases and ORS is rarely required.

Home-based ORS substitutes: Following fluids may be used as temporary alternatives of ORS, in order of preference:

- ***Salt and sugar solution (SSS)*** by mixing a two-finger pinch common salt (~0.8 gm) and one heaped tsf of sugar (~8 gm) in one glass of water (~200 ml). However, sodium/sugar content in SSS is unreliable and it should be avoided as far as possible, unless WHO-ORS is not readily available.
- ***Food-based home fluids***, e.g. salted-rice kanji, dalwater, butter-milk, lemon sherbat or coconut water may be used as adjuvant or temporary alternative for ORS. However, these fluids have no definite electrolyte concentrations and start fermenting after 6–8 hours in tropical climate.

Plain glucose water may cause osmotic diarrhea and should never be used as ORS, as also the sweet tea, coffee, canned fruit juices and carbonated drinks.

Parenteral fluid therapy is required in cases with—(a) severe dehydration, (b) persistent vomiting/abdominal distension, and (c) altered sensorium; and aims to correct fluid/electrolyte deficit till minimum safe limit, when ORS may be continued for further correction and maintenance. Some important aspects of parenteral fluid therapy in diarrrhea are as follows:

- ***Route:*** Although a secure IV access is must for parenteral fluid administration, intra-osseous infusion (Ch 32.3) may be used for rapid fluid correction in emergency, till IV access is obtained. Nasogastric infusion (20 ml/kg/hr) is also useful in this situation.
- ***Composition:*** Ringer lactate (Na^+ 131 mEq/L) is preferred choice for parenteral fluid therapy in diarrhea, though normal saline (Na^+ 154 mEq/L) may also be used as an alternative. *Plain dextrose fluids are ineffective and may aggravate hyponatremia.* Potassium (2 mEq/kg; upto maximum 40 mEq/L) must be added in IV infusion, but only after baby has passed urine, to avoid hyperkalemia.
- ***Amount*** of fluid infusion depends on the severity of dehydration. **WHO-Plan C** provides necessary guidelines for routine IV fluid volumes **(Table 14.17)**.
- ***Monitoring:*** All cases on IV fluids should be closely monitored to decide changing needs for fluids/electrolytes, possibility of switch-over to ORS and ***complications***, e.g. overhydration, electrolyte disturbances, infection, thrombophlebitis or local extravasation.

TABLE 14.17: WHO Plan C - IV fluid therapy in diarrhea

Age of child	*Volume and rate of infusion*
Infants	30 ml/kg in 30 minutes, followed by 70 ml/kg in 2.5 hours
Post-infancy	30 ml/kg in 1 hour, followed by 70 ml/kg in 5 hours

II. Specific anti-diarrheal therapy includes: (a) antimicrobial agents, (b) zinc supplements, (c) prebiotics or probiotics, and (d) antisecretory agents, e.g. racecadotril. Others antidiarrheal agents like *adsorbents/binding agents* (kaolin, pectin) are no longer used and *antimotility agents* (loparamide, diphenoxylate) are contraindicated in children due to risk of paralytic ileus.

- ***Antimicrobial therapy:*** Since most cases of acute diarrhea are viral and self-limiting, empirical antimicrobial therapy is of limited use and may lead to development of chronic carrier state or antibiotic-associated diarrhea. However, antimicrobials are indicated in: (a) suspected cholera or bacillary dysentery, (b) co-existing septicemia or systemic infections, and (c) toxic, malnourished or immunodeficient children.

  Some commonly used antimicrobial agents in diarrhea, based on the standard treatment guidelines of IAP (2022) are given in **Table 14.18**.
- ***Zinc supplementation*** has been shown to promote mucosal healing and reduce the severity and duration of diarrhea. WHO/IAP/GOI strongly recommend elemental zinc supplements to all children with diarrhea as PO 20 mg/day (10 mg/day in infants <6 months of age) for 14 days.
- ***Probiotics and prebiotics*** have a potential role in treatment of childhood diarrhea, specially antibiotic-

TABLE 14.18: Antimicrobial therapy in bacterial diarrhea

Shigella	IV Ceftriaxone 50 mkd × 2–5 days PO Cefixime 8 mkd × 2–5 days PO Ciprofloxacin 20–30 mkd × 2–5 days
Salmonella*	IV Ceftriaxone 50 mkd × 2–5 days PO Azithromycin 10 mkd × 3 days PO Ciprofloxacin 20–30 mkd × 2–5 days
ETEC	PO Azithromycin 10 mkd × 3 days PO Cefixime 8 mkd × 5 days
Cholera	PO Doxycycline 2–4 mkd single dose** PO Azithromycin 20 mkd single dose PO Ciprofloxacin 20 mkd single dose
Amoebiasis	PO Metronidazole 30 mg mkd × 5 days
Giardiasis	PO Metronidazole 15 mg mkd × 5 days

mkd: mg/kg/day, **ETEC**: Enterotoxigenic *E. coli*
*Non-typhi, Only in high-risk children ** above 2 years of age
Source: Standard treatment guidelines for acute watery diarrhea, IAP 2022.

associated diarrhea. These agents inhibit the growth of pathogenic flora and promote re-colonization with normal non-pathogenic flora.

Probiotics are viable bacteria, e.g. lactobacilli or yeasts, e.g. saccharomyces, present in fermented dairy products, e.g. curd, yogurt, lassi, etc. or available commercially. These agents: (i) competitively inhibit the binding sites for pathogenic bacteria, (ii) acidify gut to inhibits pathogenic growth, (iii) restore non-pathogenic flora, (iv) stimulate secretory IgA production, and (v) modify toxin receptors in gut. Efficacy of probiotics depends on the dose and the strain/s used for therapy, which is not yet standardized.

Prebiotics are food ingredients, e.g. banana, sorghum, lactulose, bran, isabgol, etc., which largely remain undegraded in gut and: (a) stimulate growth of normal gut flora, (b) prevent growth of pathogenic organisms by acidification of gut, and (c) maintain epithelial integrity.

- ***Anti-secretory agents:*** *Racecadotril* (PO 1.5 mg/kg/dose q8hr)-an oral encephalinase inhibitor, may be useful to reduce the stool volume in *secretory diarrhea*, though there is no uniform consensus regarding its use in children. It prevents inactivation of endogenous encephalins-cyclic AMP inhibitors in gut, thus reducing active fluid/electrolyte secretion from gut.

III. *Nutritional management:* Diarrhea is major precipitating factor for malnutrition in children. Hence, it is recommended that:

- Breastfeeding should be continued uninterrupted.
- Contrary to general perception, no dilution of animal/formula milk is necessary in top-fed children during diarrheal episodes.
- Children on regular diet should be fed with small frequent meals of energy-dense foods.
- Post-recovery, oral intake should be enhanced to 125% of normal caloric requirements.

National Control Of Diarrheal Diseases Programme (NCDDP)

NCDDP, started as a disease-specific program in 1978 is currently a component of *Reproductive, Maternal, Newborn, Child and Adolescent Health strategy* (RMNCH+A), delivered as per Integrated Management of Neonatal and Child Illnesses (IMNCI) guidelines.

Components: Important activities under this program include:

- *Standard cases management guidelines* for general use **(Fig. 14.15)**.
- *Promotion of preventive measures*, e.g. breastfeeding, hygiene and ORS therapy.
- *Free supply of WHO-ORS*, with a printed logo for easy identification **(Fig. 14.16)**.

Fig. 14.16: ORS logo.

- Setting-up of *diarrhea training and treatment units* (DTTUs)
- Research, surveillance and manpower training

Diarrhea training and treatment units (DTTUs) have been established under this program at medical colleges and major hospitals to: (a) streamline practice of standard cases management guidelines on regular basis, (b) train faculty members, medical students and other health personnel, and (c) educate mother about home management of diarrhea, including demonstration of ORS making and administration.

Mini-DTUs and *ORT corners* have been established at smaller primary health centers to implement standard cases management guidelines and maternal education.

Despite these targeted efforts, NFHS-5 (2019–21) revealed that ORS and Zinc supplements were received by only 60% and 30% of under-five children respectively, who had diarrhea in preceding two weeks of survey.

14.11 PERSISTENT DIARRHEA

Persistent diarrhea refers to "*prolonged continuation of an acute diarrheal episode beyond 14 days*", usually due to diarrhea-induced gut injury.

While two terms-*persistent diarrhea* and *chronic diarrhea* are often used interchangeably, later one is usually a manifestation of primary malabsorption defect–a heterogeneous group of congenital or acquired gut disorders, characterized by impaired digestion and/or absorption of ingested nutrients and discussed in next chapter 14.12.

Some important differences between persistent and chronic diarrhea are given in **Table 14.19**.

Etiopathogenesis: Some amount of transient gastrointestinal mucosal injury is inevitable in acute diarrhea, which usually recovers rapidly and spontaneously after cessation of primary insult.

Persistent diarrhea indicates—(a) *excessive mucosal damage* during acute phase, or (b) *impaired repair* during recovery, with or without persistence of infection.

Disaccharides (Lactose) intolerance is one of the leading cause of persistent diarrhea, discussed later in chapter.

TABLE 14.19: Persistent vs chronic diarrhea

	Persistent	*Chronic (MAS)*
Duration	>2 weeks	Longer
Cause	Post-infective	Non-infective*
Common age	<2 years	Any
Malabsorption	Effect	Cause
Course	Persistent	Recurrent
Stools	Watery	Cause-specific
Dehydration	Common	Uncommon
Malnutrition	Risk factor	Effect

*although secondary infection is common

Risk-factors for persistent diarrhea include—(a) younger age <2 years, (b) severe malnutrition, (c) vitamin A deficiency, (d) top-feeding, (e) bacterial diarrhea due to enteropathogenic organisms, (f) milk–protein allergy, (g) co-existing systemic infection.

Clinically, apart from persistent diarrhea, these cases also present with secondary complications, e.g. (a) dehydration, (b) dyselectrolytemia, (c) progressive malnutrition. Secondary lactose intolerance is common.

IMNCI classifies these cases as: (a) severe persistent diarrhea with dehydration, and (b) persistent diarrhea without dehydration.

Diagnostic evaluation in these cases aims to identify risk–factors for persistence of diarrhea and its complications. Specific tests for malabsorption (Ch 14.12) though frequently abnormal, are usually unnecessary in these cases, as malabsorption is the effect and not the cause of persistent diarrhea. Important diagnostic investigations include:

- *Stool examination* for pH and reducing sugar (secondary lactose intolerance), microscopy (parasitic/protozoal etiology) and cultures for unusual pathogens, e.g. spore-forming protozoa and Candida.
- *Base-line evaluation* for secondary effects, e.g. hemoglobin (anemia), serum electrolytes, blood sugar (hypoglycemia) and blood cultures to exclude systemic infection.
- *Other investigations,* e.g. colonoscopy are indicated only in cases with intractable diarrhea.

Management of persistent diarrhea includes—(a) correction of dehydration and dyselectrolytemia*, (b) treatment of co-infections and metabolic complications*, (c) nutritional management, and (d) micronutrient supplementation. (*as in acute diarrhea).

- **Nutritional management** is the cornerstone of therapy in persistent diarrhea, considering inevitable development of secondary malabsorption defects after prolonged mucosal injury. *Lactose intolerance* is the predominant absorption problem in these cases, while more severe cases may also develop fat intolerance. Protein absorption is often preserved till late stages.

Fig. 14.17: Dietary plan for persistent diarrhea.

In infants <4 months, persistent diarrhea is unlikely and continuation of breastfeeding is the best option in these cases. In top-fed children of this age group, a lactose-free formula may be used for 1–2 weeks to overcome problem of lactose intolerance.

In older infants and children, dietary management depends on the amount of lactose-load that they can tolerate. Most children, despite moderate lactose intolerance, tolerate low-lactose diet, if given in small frequent feeds.

Accordingly, a step-wise approach is recommended in dietary management of persistent diarrhea **(Fig. 14.17)** with three different types of therapeutic diets **(Table 14.20)** to provide nutrition, till recovery. Each diet differs in its lactose or other carbohydrate content. Success or failure of each step is assessed by change in stool frequency and weekly weight gain.

- ***Diet plan A*** (Low-lactose diet) is recommended as initial therapy to all but very severe cases and should be started as soon as baby starts accepting oral feeds. It includes feeding with low-lactose foods, e.g. milk-rice gruel, milk-sooji gruel, curd-rice, puffed rice, *dalia,* etc. in small, frequent (6–7) feeds, to provide ~110 cal/kg/day initially, which may be further gradually increased to ~150 cal/kg/day by 2 weeks. Diet A may also be given via nasogastric tube in reluctant children. Animal milk must be reduced to <50–60 ml/kg.
- ***Diet plan B*** (Lactose-free diet) is needed in children, who do not improve on diet A. This is a complete lactose-free diet with low-starch content, e.g. a cereal and glucose mixture, with egg or commercial proteins. Animal as well as human milk is eliminated totally.
- ***Diet plan C*** (Monosaccharide-based diet) is rarely required in <10% cases, who do not recover on diet B. It contains only glucose along with egg/chicken/

TABLE 14.20: Representative diets in persistent diarrhea

	Diet A	*Diet B*	*Diet C*
Milk	1/3 katori	–	–
Egg *or* (chicken)*	–	1¾ (2½) tsf	2½ (5) tsf
Puff rice powder#	4 tsf	2 tsf	–
Sugar	½ tsf	¾ tsf	¾ tsf
Oil	½ tsf	1 tsf	1 tsf
Water (add to)	100 ml	100 ml	100 ml
Calories	96	78	60
Proteins	2.4	2.3	3

*volume in parentheses is for chicken, #can be substituted by cooked rice

commercial proteins, with added oil. Cereals are also completely eliminated from the diet, along with milk.

Change-over from one to other diet plan depends on clinical response, as follows:

Step-up (Diet A>B>C) is indicated in cases with: (a) marked increase in stool frequency (>10/day) after at least 48 hours of initial diet, (b) appearance of dehydration anytime, or (c) failure of weight gain till 7th day. In rare cases of failure despite diet C, total parenteral nutrition is indicated.

Step-down (diet C>B>A> home diet) should be allowed only after 7 days of satisfactory clinical response, to permit enough time for mucosal recovery.

A baby is fit for discharge, only when: (a) stools are of normal consistency with frequency of <2/day, (b) home-diet has been introduced and well tolerated, (c) weight gain is satisfactory.

- **Micronutrient supplementation** is essential in all cases of persistent diarrhea, usually in double doses of regular RDA. However, iron should be added only after control of diarrhea.

Essential micronutrient supplements include: (a) single dose of Vitamin A 2,00,000 IU (1,00,000 IU in infants), and (b) oral zinc 20 mg/day (10 mg/day < 6 months of age) for 2 weeks. Some workers also advise potassium and magnesium supplements in early stages, given orally or parenterally.

Disaccharide (lactose) intolerance: Disaccharidase enzymes, essential for digestion/absorption of various carbohydrates are located in the brush borders of epithelial cells of small intestinal mucosa. While congenital deficiency of these enzymes is very rare (commonest being sucrase-isomaltase deficiency), secondary deficiency is common due to acquired insults to intestinal epithelium, e.g. in diarrhea, malnutrition and prolonged antibiotic therapy.

Lactose intolerance is the commonest cause of persistent or intractable diarrhea in Indian children, due to deficiency of *lactase*-an enzyme, essential for lactose absorption.

Etiology of lactose intolerance may be divided into three categories:

a. *Secondary lactase deficiency* due to transient mucosal injury in acute diarrhea, malnutrition or prolonged antibiotic therapy is the commonest cause of temporary lactose intolerance in childhood.
b. *Congenital or inherited lactase deficiency* is known but extremely rare.
c. *Ontogenic lactase deficiency:* Normally, lactase levels rise in late fetal life, remain high during first 2–3 years and then decline gradually due to reducing milk intake in diet. Hence, ontogenic lactose intolerance is common in preterms, early infancy and children >3 years. Indians have lower lactase levels than western population, probably due to less milk consumption.

Pathogenesis: In lactase deficiency, lactose cannot be hydrolyzed into absorbable monosaccharides, i.e. glucose and galactose. Consequent accumulation of unabsorbed sugars in distal intestines leads to:

- *Hyperosmolarity* of luminal contents causing osmotic diarrhea, and
- *Fermentation* of sugar into gases (H_2, CO_2, and methane) and organic acids, causing gaseous abdominal distension, borborgymi and acidic, frothy stools.

Clinically, most cases present as unusual persistence of diarrhea after an acute viral episode, with:

- Watery, frothy, explosive stools,
- Bloating abdominal distension and borborgymi,
- Perianal excoriation, due to acidic stools.

Laboratory diagnosis depends on:

- *Acidic pH* of stools (normally alkaline),
- *Reducing sugars in stools* on Benedict test*
- *Breath-hydrogen test* revealing high hydrogen content in expired air (>15 ppm) due to excess carbohydrate fermentation in gut.
- *Enzyme assays* on mucosal biopsy, though rarely necessary.

****Benedict test***: Add 8–10 drops of saline-stool suspension in 5 ml of Benedict reagent and heat the mixture. A change of color from blue to orange or brick-red indicates presence of reducing sugar. Prior hydrolysis of stool sample with hydrochloric acid is needed to detect presence of sucrose, which is not a reducing sugar.

Management of these cases includes:

- *Reduction in lactose load:* Lactose intolerance is almost always secondary, transient and partial. Hence, management of these cases includes partial or complete withdrawal of milk for 5–7 days, to allow recovery of damaged brush borders and enzyme activity. Although most cases tolerate low-lactose diet (Diet A), severe/refractory cases may need lactose-free diet (Diet B) for 2–3 days, followed by gradual re-introduction. Soya-milk can also be used during this period.

- *Supplementation of lactase* enzyme in diet, by adding specific lactase preparation (2–3 drops in one litre of milk) 2–3 hours before consumption is useful, provided the milk is not re-heated before consumption. Use of yogurt/curd, which contains lactase-producing bacteria, is also beneficial.

14.12 MALABSORPTION SYNDROMES (CHRONIC DIARRHEA)

Malabsorption syndrome (MAS) is a *heterogeneous group of acquired or congenital disorders characterized by impaired digestion and/or absorption of all or some of the ingested dietary nutrients*. Clinically these disorders present with: (a) chronic or intractable diarrhea, (b) failure to thrive, and (c) signs of multiple or specific nutrient deficiencies, e.g. steatorrhea, edema, anemia, vitamin deficiencies, etc.

Transient malabsorptive defects secondary to post-infective diarrhea-induced mucosal injury (persistent diarrhea) are excluded from this definition.

Etiopathogenesis: Proximal half of small intestine is the most important site for absorption of proximate principles, e.g. proteins, fats and carbohydrates, while water and electrolytes are absorbed throughout its length. Bile salts and vitamin B_{12} are selectively absorbed at terminal ileum. Iron is mainly absorbed in duodenum and proximal jejunum.

Intraluminal digestion depends on exocrinal pancreatic enzymes (lipase, trypsin, chymotrypsin and others) and bile-salts from liver. Two important intestinal enzymes from proximal intestinal mucosa-secretin and cholecystokinin, released in response to the arrival of food, provoke these exocrine secretions.

Digestion and absorption of ingested nutrients is a complex and continuous process (Ch 14.1), dependent on the adequacy of-(a) digestive enzymes, (b) absorptive gut surface and (c) specific transporter mechanisms and enzyme activity, necessary for absorption of nutrients. These functions are deranged in MAS **(Table 14.21)** with impaired absorption of one or more nutrients.

According to the type of absorptive defects, MAS may be broadly divided into two categories:

a. *Generalized MAS* involving defective assimilation of multiple nutrients, due to loss of intestinal surface, mucosal integrity or motility disorders. Fat malabsorption is the earliest event in generalized MAS, characterized by *steatorrhoea*, i.e. foul and bulky stools with fat globules.

b. *Selective MAS*, limited to malabsorption of only one or two nutrients, due to specific defects in absorption mechanisms or transport enzymes, e.g. fat malabsorption in biliary disorders, protein malabsorption in amino acid transport defects, zinc malabsorption in acrodermatitis enteropathica, etc.

TABLE 14.21: Causes of chronic diarrhea (MAS)

Generalized malabsorptive states
- Chronic non-specific (Toddler's) diarrhea
- Impaired intestinal mucosal integrity
  - *Infective:* Post-enteritis, giardiasis, tuberculosis
  - *Allergic:* Food allergy, celiac disease, T. sprue
  - *Inflammatory bowel diseases:* Crohn disease, U. colitis
  - *Drugs:* Methotrexate, neomycin
- Reduced absorptive surface
  - Congenital short bowel syndrome
  - Surgical resection of large bowel segment
- Motility disorders (bacterial overgrowth)
  - Stagnant loop syndrome
  - Sub-acute intestinal obstruction
  - Irritable bowel syndrome
  - *Iatrogenic:* Laxatives, cholestyramine, antibiotics

Selective malabsorptive states
- Intestinal enzyme defects
  - *Carbohydrates:* Disaccharidase (lactase) deficiency
  - Amino acid transport defects, e.g. Hartnup disease
  - *Fat:* Abetalipoproteinemia
  - *Vitamin:* Pernicious anemia, folate malabsorption
  - *Minerals:* Chloride-loosing enteropathy, A. enteropathica
- Pancreatic disorders (fat and protein)
  - Cystic fibrosis
  - Chronic pancreatitis
  - *Isolated enzyme defects:* Lipase, trypsinogen
- Hepatic disorders (fat and fat-soluble vitamins)
  - *Cholestatic disorders:* Biliary atresia, gallstones
  - Chronic liver disease
  - Primary bile acid absorption defects

*U. Colitis: Ulcerative colitis,
A. enteropathica: Acrodermatitis enteropathica

Diagnostic evaluation in MAS aims not only to identify possible etiology but also the extent of its effect on health, e.g. nutrient deficiencies. It includes:

- **Clinical evaluation,** with special reference to:
  - Age of onset,
  - Relationship with introduction of cow-milk, wheat, egg, etc. in diet
  - Preceding history of acute/recurrent diarrhea,
  - Aggravation on selected foods (allergic)
  - Family history (enzyme defects, celiac disease)
  - Past history of GIT surgery/disease/drugs
  - Presence of abdominal pain, melena, vomiting, etc.
  - Signs of selective nutrient deficiencies, e.g. edema.
- **Stool characteristics**
  - Foul-smelling and bulky (fat-malabsorption)
  - Large and watery (congenital channelopathies)
  - Frothy, explosive diarrhea (carbohydrate malabsorption).

  Stools are generally large and pale with offensive odor in small bowel diarrhea, while small volume, often associated with blood and mucus in large bowel disorders.

- **Malabsorption tests:** Some important tests for malabsorption are as follows:
  - ***Fat malabsorption*** is characterized by bulky-foul smelling stools with *steatorrhoea*, i.e. presence of fat globules visually or on microscopy after sudan-red staining. *Quantitative estimation of total fat excretion* over 72 hours on a controlled diet (>5 gm/day) is a sensitive indicator of fat malabsorption.
  - ***Carbohydrate malabsorption*** is characterized by *watery and frothy stools* with *acidic pH* (<5.6) and *positive Benedict test* for reducing sugar. As sucrose is not a reducing sugar, stool sample should be hydrolyzed by hydrochloric acid before testing.
  - ***Protein malabsorption*** cannot be assessed directly as proteins are normally present in stool, though most of them are derived from bacterial sources rather than dietary proteins. Low *serum albumin* levels and high spot *stool 1-antitrypsin levels* indicate protein-loosing enteropathy.
  - ***D-xylose absorption test***: D-xylose is a pentose sugar absorbed mainly in upper small intestines. A blood concentration of < 25 mg/dl of xylose after one hour of oral dose (14.5 gm/m^2) indicated proximal bowel lesion.
  - ***Positive Schilling test*** despite intrinsic factor supplementation, indicates terminal ileum disease, as vitamin B_{12} is absorbed in distal bowel (Ch 19.4.2).
- **Etiological investigations:** Considering the diverse etiology, investigations in chronic diarrhea are recommended in a sequential manner **(Table 14.22)**.

TABLE 14.22: Investigations in MAS

Step I. *(Preliminary screening tests)*
- ***Stool examination***
  - Gross for fat globules, blood and volume
  - Microscopic for fat globules, ova and cysts
  - Biochemical for pH, reducing sugar
  - Cultures for common/opportunistic infections
- ***Blood examination***
  - CBC/PS for typing of anemia, acanthocytes
  - S. proteins for hypoproteinemia
  - Baseline electrolytes
- ***Radiological investigations***
  - Contrast barium studies
  - USG abdomen

Step II. *(Specific diagnostic tests)*
- Quantitative 72-hour fat excretion for steatorrhoea
- Breath hydrogen test for lactose intolerance
- Stool electrolytes for Cl-loosing enteropathy
- Sweat chloride test *for* cystic fibrosis
- D-xylose absorption test *for* proximal bowel disease
- Schilling test *for* distal bowel disease
- Upper GIT endoscopy/small bowel biopsy
- Colono/sigmoidoscopy/biopsy

Step III *(Rarely warranted)*
- *Hormonal studies:* VA peptides, gastrin, secretin, etc.

Management of MAS depends on etiology, though general principles are same as for persistent diarrhea, including nutritional management.

Celiac disease *(Gluten-sensitive enteropathy, nontropical sprue)* is one of the commonest causes of chronic diarrhea and MAS in children above 2 years.

Etiologically, celiac disease is a T-cell mediated autoimmune inflammatory disorder, representing small-bowel hypersensitivity to *gliadin fraction of gluten*, i.e. primary wheat protein. *Tissue Transglutaminase* (tTG) is an enzyme present in intestinal epithelium, which deamidates gliadin to stimulate the immune system and initiate inflammatory process in celiac disease.

Genetic predisposition is well known as: (a) over 90% cases are positive for HLA-DQ2 or DQ8 haplotype, (b) similar family history is present in ~10% cases, (c) nearly 100% concordance in monozygotic twins, and (d) higher risk in some genetic disorders, e.g. Down syndrome, Turner syndrome, diabetes mellitus, autoimmune thyroiditis, etc.

Clinically, these children present at ~6 months of age after introduction of wheat-products in complementary diet with: (a) chronic diarrhea as large, pale bulky stools, (b) recurrent vomiting, and (c) failure to thrive; with intermittent worsening of symptoms (*Celiac crisis*). Onset of diarrhea before introduction of wheat products is against the diagnosis of celiac disease.

On examination, abdominal distension, short stature and generalized wasting are consistent features, along with pedal edema due to hypoproteinemia and clubbing in severe cases. Extra-intestinal manifestations, specially refractory iron deficiency anemia, are common in older children. Silent disease may be present in first-degree relatives with asymptomatic histopathological changes.

Diagnosis is confirmed on small bowel biopsy to demonstrate characteristic villous atrophy along with repeat biopsy 1–2 years after gluten withdrawal, to show normalization of histology.

However, *quantitative serum anti-tissue transglutaminase IgA antibody* (IgA-tTG) is the screening test of choice as per ESPGHAN 2020 guidelines with sensitivity and specificity of 91–100%. Diagnosis of celiac disease can be made without duodenal biopsy, if—(a) IgA-tTG titers are >10 times of upper normal limit, (b) anti-*endomysial antibody* is also positive, and (c) there is definite clinical response to gluten-free diet. Biopsy is necessary for diagnosis in absence of quantitative IgA-tTG values.

Treatment includes exclusion of gluten-containing cereals (wheat, rye, barley) from diet, which provides symptomatic relief in 2–4 weeks with resumption of weight gain. Wheat is the major source of gluten in diet and all wheat-based foods should be completely avoided in celiac disease, replacing them with rice or maize-based foods. A short course of steroids may be indicated during celiac crisis.

Tropical sprue is a disease of unknown etiology (probably hypersensitivity), with diffuse chronic inflammation of small intestines, seen in many tropical countries including India. Intestinal microbial infection has been proposed as the initiating even, which leads to mucosal injury, gut stasis and bacterial overgrowth.

Clinically, these cases present with intermittent watery diarrhea/steatorrhea, severe anorexia, failure to thrive, multiple nutrient deficiencies and mild fever. Small bowel biopsy may be needed to exclude celiac disease and other causes of MAS. Most episodes respond well to antibiotics and folate/vitamin B_{12} supplementation.

Cow-milk protein allergy (CMPA) is common in developed countries (2–5%) and is being increasing recognized as an important cause of chronic diarrhea in under-five Indian children.

Etiologically, CMPA is more common in children with similar family history and top-feeing in early infancy. It may present as—(a) IgE-medicated allergic reaction with urticaria, vomiting and hypotension soon after the consumption of milk, or (b) delayed hypersensitivity reaction with long indolent course of intestinal malabsorption.

Clinically, CMPA presents with recurrent bloody or watery diarrhea on cow milk exposure, occasionally associated with GERD, hematemesis and severe anemia. Respiratory and skin allergies are present in ~30–50% cases.

Diagnosis must be suspected in a case with family history and eosinophilia and confirmed by the *challenge test*, i.e. disappearance of symptoms on elimination of cow-milk from diet for 1–2 weeks, which reappear on re-exposure. Positive skin prick test and elevated IgE levels suggest IgE-mediated disease.

Treatment involves removal of all animal milk and milk-products from the diet, replaced by extensively hydrolyzed formula (EHF) or soya milk, though ~10% may have concomitant soy allergy.

Nearly, half of the children outgrow CMPA by 1 year and >95% by 5 years of age. Breastfeeding may be continued despite mild symptoms, though mother must be advised to avoid consuming milk/milk-products during lactation period. Micronutrient supplements are necessary and trial-introduction of milk feeds should be attempted after first year.

Food allergy, other than CMPA, are uncommon contrary to popular belief and usually present with extra-intestinal rather than intestinal manifestations. All adverse reactions to foods are not allergies.

Commonly implicated allergens include egg, peanuts and food-additives, e.g. preservatives (sodium meta bisulfite) coloring agents (tartrazine) and flavouring agents (monosodium glutamate or Azinomoto).

Clinical spectrum of food allergy is extremely wide, including gastrointestinal, respiratory and cutaneous manifestations, including serious *anaphylactic* reactions.

TABLE 14.23: D/D Crohn disease vs ulcerative colitis

	Crohn disease	*Ulcerative colitis*
Site of lesion	Anywhere in GIT	Colon only
Abd. pain	++	+
Dysentery	+	++
Perianal lesions	+++	–
Serology	ASCA+ve	P-ANCA+
Barium studies	String sign	Lead pipe colon
Endoscopy	Skip lesions	Diffuse colitis
Biopsy	All layers involved	Limited to mucosa

Diagnosis depends on—(a) appearance of symptoms after introduction of suspected food item in diet, (b) relief of symptoms after elimination of that item, and (c) reappearance of symptoms on re-introduction in the diet (*challenge test*). However, challenge tests should be avoided in cases with severe allergic reactions. Skin-prick tests are unreliable to identify the causative food, unless substantiated by strong cause-effect relationship.

Management of food allergy includes—(a) symptomatic treatment of acute attacks, and (b) elimination of suspected food item from diet, but only if strong correlation has been established.

Inflammatory Bowel diseases (IBDs) includes two important intestinal diseases-*Crohn disease (CD)* and *Ulcerative colitis (UC)*, both characterized by chronic mucosal inflammation with intermittent exacerbations and remissions **(Table 14.23)**. Another ~10% cases cannot be classified in these two categories and are termed as *Indeterminate colitis*.

Early onset IBD in young children is generally considered as a different phenotype than adult-onset disease, due to strong genetically attributable risk.

Incidence: Children and adolescents years account for ~25% of all IBDs with mean age of presentation as ~11–12 years.

Etiologically, IBDs represent inappropriate immune response to environmental factors in a genetically susceptible host as:

- Many causative genes have been identified for IBD, e.g. *NOD2* and *IBD5, and*
- More than half of these cases have specific antibodies, e.g. anti-*saccharomyces cerevisiae* antibodies (ASCA) in CD and perinuclear antineutrophil cytoplasmic antibodies (P-ANCA) in UC.

Pathologically, CD may involve *any part* of gut, including terminal ileum and upper colon (50–70%), upper GIT (30–40%) and perianal lesions (15–20%). In contrast, lesions in UC are usually limited to colon and rectum, sparing rest of the GIT.

Further, UC lesions are in continuity with each other, while those in CD have normal intervening mucosa (*skip lesions*).

Clinical manifestations of both IBDs usually begin in late adolescence, with a waxing and waning course of variable severity, as follows:

- Recurrent crampy abdominal pain with sticky diarrhea dominates in CD, while UC usually presents with recurrent dysentery and tenemus.
- Constitutional symptoms, e.g. fever, anemia, weight loss, easy fatiguability are present in both IBDs, though growth failure is more prominent in CD.
- Extra-intestinal manifestations are present in 20–30% of both IBDs, including arthritis, uveitis, aphthous ulcers, cholangitis, erythema nodosum, etc. Clubbing is common.
- Perianal lesions, e.g. fistula, abscess, tags, etc. and complications like subacute obstruction due strictures or deep seated abscesses are common in CD.

Diagnosis must be considered in any case with history of recurrent/persistent abdominal pain and/or dysentery/sticky diarrhea, for >4 weeks. Inflammatory markers, e.g. ESR, CRP are usually elevated. Fecal Calprotectin level is a reliable screening test to differentiate IBD from functional abdominal pain.

Confirmation requires: (a) upper GI endoscopy with biopsy, (b) colonoscopy with ileal intubation and biopsy in all cases, with CT/MRI to assess the severity of IBD. Multiple biopsies are required from different sites for correct diagnosis. Important investigational differences between CD and UC are as follows:

- Endoscopy reveals deep, irregular ulcers with normal intervening mucosa (*skip lesions*) in CD and concentric diffuse colitis with acutely inflamed and friable mucosa in UC.
- Barium studies may show thick ileal folds with narrowed lumen (*string sign*) and linear ulcers (*cobblestone appearance*) in CD and loss of haustral markings with thickening of mucosal folds (*lead-pipe colon*) in UC.
- Histopathology reveals *transmural* inflammation of all intestinal layers with non-caseating granuloma in CD and only mucosal involvement with cryptitis or crypt abscesses in UC.

Management includes: (a) treatment of acute attacks, and (b) maintenance of remissions, as follows.

Ulcerative colitis in acute phase is generally treated with a 5-Aminosalcylate (5-ASA) drug, e.g. S*ulfasalazine* (PO 50–75 mg/kg/day q8hr), though steroids, e.g. prednisolone (PO 1–2 mg/kg/day q24hr) are used in severe cases, till remission is achieved. Rare refractory cases require treatment of acute attack with monoclonal antibodies, e.g. infliximab *or* calcineurin inhibitors (Cyclosporine/Tacrolimus), under expert guidance.

Once remission is achieved, it may be maintained with long-term use of 5-ASA or immunomodulators, e.g. azathioprine or 6-mercaptopurine in cases with ASA intolerance or poor response. Rare cases need Infliximab for maintenance.

*Surgery i*s indicated in selected cases of: (a) treatment failure or treatment dependence, or (b) toxic megacolon, with a two-step procedure of colectomy and pouch formation with ileostomy as the first step, followed by ileostomy closure.

Crohn disease in acute phase is treated with steroids, e.g. Prednisolone (PO 1–2 mg/kg/day q24hr) for 2–4 weeks followed by slow tapering over 8 weeks. Exclusive enteral nutrition (EEN) is the treatment of choice for only luminal CD, while metronidzaole and/or ciprofloxacin are used for perianal lesions. Monoclonal antibodies, e.g. Infliximab may be used in non-responsive cases.

Once achieved, remission may be maintained with immunomodulators, e.g. azathioprine, 6-mercaptopurine or methotrexate (with folic acid). Rare cases need Infliximab for maintenance.

Surgery is indicated in non-responsive localized CD resect areas with macroscopic disease, e.g. ileocolonic area with right hemicolectomy. Surgery is also needed for intestinal strictures, perforation, intra-abdominal abscesses and perianal fistula. However, recurrence is common.

Prognosis: Most IBDs respond well to medical treatment during initial attacks, though intermittent exacerbations are common. Toxic megacolon is the most important complication in acute stage. Some cases may develop colonic cancers after 10–15 years.

Abdominal tuberculosis or "*Koch's abdomen*" refers to *tubercular involvement of intestines, peritoneum and mesenteric lymph nodes,* excluding involvement of other abdominal organs, e.g. kidney, gonads and adrenals.

According to site of localization, it may be classified as peritoneal, nodal and intestinal **(Table 14.24)**. Intestinal infection tends to localize at *ileocaecal region* due to relative stasis and large lymphoid tissue.

Pathogenesis: GIT tuberculosis is usually acquired hematogenously during intermittent bacteremia from a pulmonary focus, though abdominal lymph nodes may be involved via retrograde lymphatic spread from mediastinal nodes. Direct GIT infection, as seen in Bovine tuberculosis, is very rare in India.

TABLE 14.24: Types of abdominal tuberculosis

- **Peritoneal**
  - Exudative peritonitis (TB ascites)
  - Adhesive or plastic peritonitis
  - Miliary peritonitis
- ***Nodal:*** Mesentric TB *(T. mesenterica)*
- **Intestinal**
  - Hypertrophic ileocecal
  - Ulcerative

Clinical presentation depends on the site and nature of lesions. Intestinal tuberculosis present with:

- Intermittent episodes of diarrhea/constipation, due to subacute obstruction,
- Abdominal pain and/or distension with typical *doughy* feel and presence of ascites,
- Constitutional features, e.g. low-grade fever, anorexia and weight loss.

Hepatomegaly, ascites and abdominal lump suggestive of mesenteric lymph nodes or ileocaecal mass may be present.

Complications, e.g. intestinal obstruction, fistula formation, peritoneal cold abscesses are common while perforation and hemorrhage is rare in intestinal disease.

Diagnosis usually rests on USG or contrast-enhanced CT (CECT) showing (a) concentric bowel thickening with contracted cecum, distorted ileocecal angle and short strictures in *intestinal disease*, (b) conglomerate lymph nodes of >1 cm with central necrosis in *nodal disease,* and (c) mesenteric thickening >15 mm with ascites in *peritoneal disease*. Rarely, focal granuloma may be present in liver or other organs. Barium meal with follow-through has been conventionally used for diagnosis of intestinal tuberculosis, though rarely used at present **(Fig. 14.18)**.

Peritoneoscopy is highly sensitive and specific (>93% and 98% respectively) for diagnosis of peritoneal tuberculosis, showing hyperaemic and thickened peritoneum, whitish miliary nodules, adhesions and ascites.

All attempts should be made to confirm bacteriological diagnosis with drug sensitivity/resistance testing, from ascetic fluid or CT-guided peritoneal/node biopsy (Ch 10.13).

Fig. 14.18: Abdominal tuberculosis (barium follow-through). Note pulled-up ileocecal region with strictures. (***Courtesy:*** Dr S Malik)

Treatment includes specific antitubercular therapy according to drug sensitivity profile along with supportive treatment (Ch 10.13). Surgery is indicated in only in-(a) non-resolving intestinal obstruction, (b) perforation peritonitis, abscess or (c) fistulous communication, preferably after antitubercular therapy.

Toddler's diarrhea *(chronic non-specific diarrhea)* is the commonest and self-limiting cause of chronic diarrhea in infancy, with onset between 6 months and 3 years of age.

First morning stool is usually well formed but the frequency (4–6/day) and liquidity increases as the day progresses, sometimes containing mucus and undigested food. Dehydration or failure to thrive is typically absent. Similar family history is common and symptoms may be precipitated by teething or common infectious illnesses. Excessive ingestion of fruit juices or non-absorbable sugars has been implicated in etiology.

Diagnosis involves exclusion of more serious causes. No specific treatment is required except dietary modification (high-fibre, high-fat, low-carbohydrate diet). Problem resolves spontaneously by 3–4 years of age.

Other important but uncommon causes of MAS are as follows:

Chronic malnutrition is a common cause of MAS, due to—(a) intestinal villous atrophy, more prominent in Kwashiorkor, (b) bacterial overgrowth in upper intestine due to relative immunodeficiency, (c) suboptimal exocrinal pancreatic functions. Vitamin A supplements are beneficial to some extent in these cases.

Immunodeficiency disorders, congenital (SCID, IgA deficiency) or acquired (HIV, malignancy, iatrogenic) are emerging as important cause of chronic diarrhea and malabsorption, either due to primary disease or secondary infections. Giardiasis and rotaviral infections are common cause of chronic infective diarrhea in these cases, apart from opportunistic infections, e.g. Candida, Cryptosporidium, Isospora, CMV, *Mycobacterium avium* intracellulare, etc.

Chronic liver disease may lead to fat malabsorption due to impaired secretion of bile acid and bile salts in duodenum. Apart from primary disease, these cases present with steatorrhea and signs of fat-soluble vitamin deficiency, e.g. vitamin A (skin and ocular xerosis), vitamin E (progressive spinocerebellar degeneration with peripheral neuropathy), vitamin D (resistant rickets) and vitamin K (bleeding diathesis).

Pancreatic disorders: *Cystic fibrosis* is the commonest cause of malabsorption due to exocrinal pancreatic insufficiency, followed by *Juvenile tropical pancreatitis* (Ch 14.16). *Shwachman-Diamond syndrome* is a rare cause of pancreatic steatorrhea with failure to thrive and neutropenia or chemotaxis defects.

Cystic fibrosis is an autosomal recessive defect in salts and water secretion by epithelial cells, leading to desiccation of exocrinal secretions. While meconium ileus is the earliest presentation in ~10–20%, older cases present with steatorrhea, recurrent respiratory illnesses, salty-skin and other complications (Ch 16.10).

Structural intestinal defects are rare causes of MAS, commonest being Blind-loop syndrome and short bowel syndrome.

Blind loop syndrome denotes abnormal stasis of small intestinal contents, due to—(a) congenital malrotation, bands or diverticula, or (b) acquired postoperative adhesions or chronic inflammatory bowel disorders. Stasis allows bacterial overgrowth in upper small bowel, which deconjugate bile salts (fat malabsorption), cause brush border injury (disaccharide intolerance) and bind Vitamin B_{12} to prevent its absorption. Clinicoradiological indicators of chronic intestinal obstruction are often absent. Oral metronidazole or non-absorbable antibiotics, e.g. neomycin or gentamycin, may be used for temporary control followed by operative correction.

Short bowel syndrome with loss of at least 50% of small bowel, may be congenital or postoperative. Resultant decrease in absorptive surface leads to fat and carbohydrate malabsorption. Management of these cases is a complex issue and involves total parenteral nutrition during acute phase, followed by gradual introduction of enteral feeding. Exposure to enteral nutrients facilitates compensatory growth of remaining bowel. Non-absorbable antimicrobials, anti-motility drugs and cholestyramine may be useful in select cases. Long-term prognosis is poor unless prolonged TPN is possible to allow gradual bowel growth. Many of these patients may ultimately require small intestinal transplant.

Specific absorption/transports defects for many nutrients are known, although rare. Some important ones include:

Abetalipoproteinemia is rare autosomal recessive deficiency of β-lipoproteins, essential for chylomicron formation. These cases present with: (a) failure to thrive and steatorrhea since early infancy, (b) neuroocular manifestations beyond first decade, (c) acanthocytosis in peripheral smear and (d) abnormal lipid profile, i.e. extremely low cholesterol, LDL and VLDL levels. Treatment involves replacement of long-chain fats with medium-chain triglycerides in the diet, which do not require chylomicrons for absorption, along with fat-soluble vitamin supplements in large doses (Ch 11.6.2).

Chloride-loosing enteropathy is a rare congenital defect in ileal chloride transport, presenting as severe watery diarrhea since birth with dehydration and unique pattern of dyselectrolytemia-*hypokalemia with hypochloremic alkalosis*. Diagnosis rests on stool electrolytes with chloride content exceeding sum of the sodium and potassium contents. Treatment is supportive.

Acrodermatitis enteropathica, an inherited defect of zinc malabsorption, presents with—(a) chronic diarrhea, (b) mucocutaneous lesions, and (c) failure to thrive. Oral zinc supplements (1–2 mg/kg/d) lead to rapid improvement. (Ch 6.9)

Amino-acid transport defects are rare malabsorption defects for select amino acids, important ones including: *Cystinuria* (no diarrhea) and *Hartnup disease* (Ch 11.6.1).

Glucose-galactose malabsorption is a rare autosomal recessive defect of glucose-galactose transport across the intestinal brush borders, which presents soon after initiation of breastfeeding with chronic diarrhea, abdominal distension and dyselectrolytemia. Strict dietary restriction of glucose-galactose with use of fructose-containing formula feeds is essential for survival.

14.13 ACUTE INTESTINAL OBSTRUCTION

Acute intestinal obstruction (AIO) is a common surgical emergency in newborns and infants due to congenital malformations, though subsequently it is less common in children than in adults.

Etiologically AIO may be broadly classified as *dynamic*, i.e. mechanical obstruction to intestinal flow or *adynamic*, i.e. paralytic ileus with absent or reduced peristaltic movements **(Table 14.25)**.

Clinical presentation depends on etiology and severity of obstruction and may be acute or sub-acute, with three common features: (a) absolute or relative constipation, (b) progressive abdominal distension, and (c) persistent vomiting or increased gastric aspirate.

Signs of dehydration and dyselectrolytemia due to impaired gut absorption and increased third-space losses appear soon. Fever is a late feature, suggestive of secondary infection or colonic overgrowth of pathogens.

On examination, visible peristaltic movements with increased bowel sounds (due to increased contractility

TABLE 14.25: Causes of intestinal obstruction

- **Mechanical (Dynamic)**
  - ***Intrinsic***
    - Congenital atresia/stenosis of intestines
    - Anorectal malformations
    - Meconium ileus
    - Foreign body, e.g. coins, bezoars, worms
  - ***Intramural***
    - Intussusception
    - Hypertrophic ileocecal TB
    - Hirschsprung disease
  - ***Extrinsic***
    - Volvulus (malrotation of gut)
    - Congenital bands/strictures/loops/duplications
    - Post-inflammatory or surgical adhesion
- **Adynamic (Paralytic ileus)**
  - Septicemia
  - *Metabolic:* Hypokalemia, poisoning
  - Exhaustion (post-diarrhea, late obstruction)

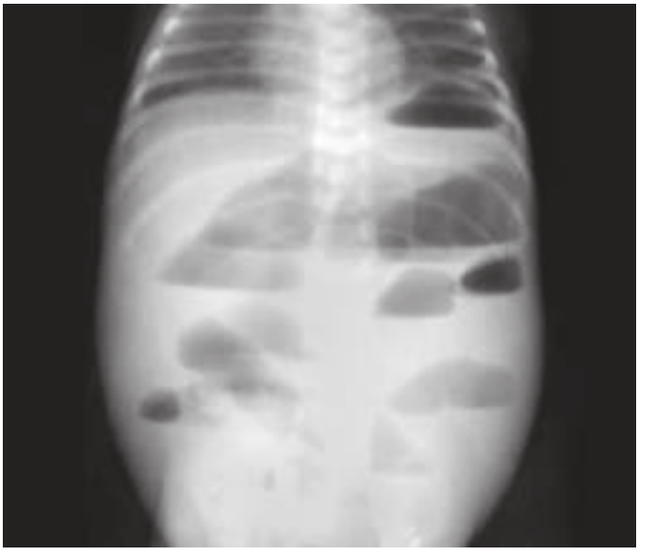

Fig. 14.19: **Intestinal obstruction: Multiple fluid levels on X-ray abdomen in standing position.**

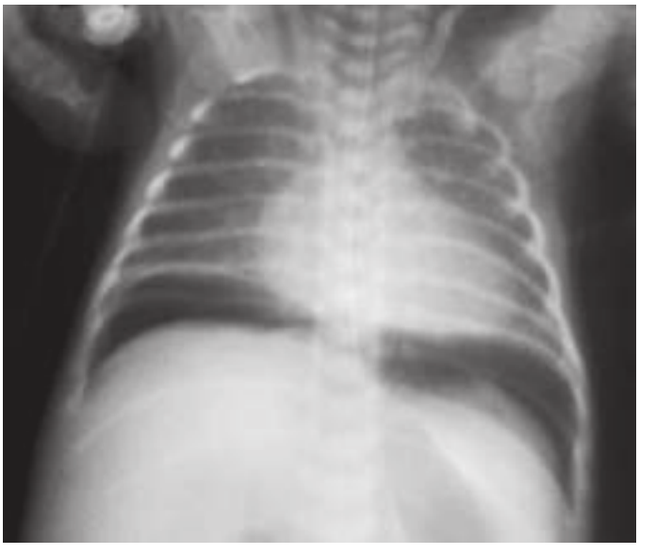

Fig. 14.20: **Intestinal perforation: Gas under diaphragm on X-ray abdomen in standing position.**

of proximal segment to overcome obstruction) indicates mechanical obstruction, while absent bowel sounds suggest paralytic ileus-either primary or after exhaustion of gut musculature in mechanical obstruction.

Diagnosis: Presence of multiple air-fluid levels on standing abdominal X-ray is diagnostic of AIO **(Fig. 14.19)**. Important etiological clues include:

- ***Age:*** While intestinal atresias, meconium ileus and necrotizing enterocolitis are dominant causes of AIO in newborns; volvulus, septic paralytic ileus and less severe congenital malformations, e.g. bands and adhesions are more common in infancy. Beyond infancy, intussusception is the commonest cause in all pediatric age groups, followed by paralytic ileus.
- ***Clinical course:*** While intestinal malformations, intussusception and volvulus present with sudden obstruction, sub-acute or recurrent obstruction in Indian children generally indicates abdominal tuberculosis, worm infestations or Hirschsprung disease.
- ***Specific clinical features,*** include presence of bile in vomiting/gastric aspirate in duodenal or high jejunal obstruction or passage of red-currant jelly per rectum in intussusception. Per-rectal exam is extremely valuable to identify Hirschsprung disease.
- ***Specific radiological features***, e.g. ground-glass appearance in meconium ileus, double-bubble sign in duodenal atresia, single grossly dilated loop in volvulus, gas under diaphragm in intestinal perforation **(Fig. 14.20)**, etc.

Management of AIO may be conservative or surgical, depending on probable cause and general condition of the patient.

Conservative management is indicated in—(i) critically sick children, (ii) surgically uncorrectable lesions, or (iii) for pre-surgical stabilization and includes: (a) gastric decompression by stopping the oral feeds and continuous nasogastric suction, (b) fluid and electrolyte correction, (c) supportive therapy including prophylactic antibiotics.

Intussusception is the commonest cause of AIO in children aged 3 months-5 years, due to telescoping of a proximal intestinal segment (*intussceptum*) into distal segment (*intussuscipiens*), leading to ileoileal or iliocolic intussusception. A causative association with rotavirus vaccine, suspected earlier, is unlikely with new-generation vaccines.

Clinically, these cases present with a triad of (a) Abdominal pain, (b) red-currant jelly stools with blood and mucus, and (c) palpable mass in some cases.

Diagnosis depends on USG showing "*Doughnut sign*" or "*Bull's eye sign*", due to central lead point encircled by concentric alternating echogenic (mucosa, muscularis) and hypoechoic (submucosa) bands. Barium enema may show "*Claw sign*" in colonic intussusception, due to irregular filling defects.

Treatment includes either conservative reduction under USG guidance by hydrostatic enema or air insufflations; or surgery in cases of failed conservative reduction or suggestion of bowel gangrene.

14.14 ACUTE APPENDICITIS

Acute appendicitis is less common in Indian children than in western counterparts, probably due to high fiber diet. It is most common in 6–10 years age group, with male preponderance (3:2).

Etiopathogenesis: Acute appendicitis usually begins with obstruction of appendicular lumen by fecoliths/worms/seeds, etc., leading to obstruction in mucus flow (mucocele) and secondary infection, followed by gangrenous necrosis of walls, perforation and peritonitis.

While perforation may be sealed by protective omentum (appendicular lump) in older children, generalized peritonitis is more common in younger children due to thinner and smaller omentum. Rarely, infection may reach appendix during hematogenous septicemia from distant sites.

Clinically, typical cases present with a specific sequence of symptoms: (a) abdominal pain, followed by (b) vomiting, followed by (c) fever, developing over 24–48 hours.

Characteristically, appendicular pain begins in periumbilical region and gradually migrates to right iliac fossa after 2–6 hours. Generalized pain indicates development of peritonitis. Constipation is common, though irritation of sigmoid colon or urinary bladder by inflamed appendix may cause diarrhea and dysuria, respectively.

Clinical examination may reveal:

- *Tenderness at McBurney's point*—the junction of lateral 1/3rd and middle 2/3rd of a line joining anterior superior iliac spine to umbilicus,
- *Psoas sign,* i.e. pain during flexion or hyperextension of the hip.
- *Tender mass in right iliac fossa*, composed of inflamed appendix, cecum, terminal ileum and omentum,
- Signs of generalized peritonitis.

Diagnosis rests on clinical suspicion with polymorphonuclear lekocytosis and must be confirmed on USG, showing dilated (>6 mm) tubular, aperistaltic, thick-walled appendix, with/without intraluminal fluid or fecoliths. USG also helps to exclude other causes of acute abdomen, including pelvic inflammatory disease in girls.

Abdominal CT scan is indicated in doubtful cases to confirm the diagnosis as well as detect/localize the perforation or intra-abdominal abscesses.

X-ray abdomen is of little value in diagnosis of appendicitis *per se*, but may reveal calcified appendicolith, air-fluid level in cecum, signs of small bowel obstruction, and pneumoperitoneum.

Treatment depends on the stage of diagnosis, as follows:

- *Non-perforated cases* need immediate appendicectomy, preferably laparoscopic, after pre-operative stabilization.
- *Perforated cases* with appendicular mass or peritonitis must be managed conservatively for 7–10 days, followed by interval appendicectomy after 10–12 weeks.

Pre-operative stabilization and conservative management includes: (a) nasogastric decompression, (b) fluid/electrolyte correction, and (c) antibiotics, including metronidazole for anerobic infections.

Prognosis: Overall mortality is <1% with surgery before perforation. Perforation is more common in younger children and carries poorer prognosis. Other complications include intra-abdominal abscesses, intestinal obstruction, and rarely, infertility due to obstruction of fallopian tubes.

14.15 PERIANAL DISORDERS

While anorectal malformations have been discussed in Ch 14.9, some important acquired problems of anorectal region are as follows:

Anal fissures, i.e. small lacerations at mucocutaneous junction of the anus, are common in infancy and early childhood due to forceful passage of hard stools in constipated children. Constipation and anal fissure are inter-related, as children with anal fissure avoid defecation to prevent pain, which further exacerbates constipation and hard stools.

Clinically, these cases present with painful defecation and passage of hard stools laced with bright-red color on the surface.

Diagnosis involves local examination revealing the fissure and sometimes a peri-anal skin tag, due to chronic inflammation. Crohn's disease must be excluded in cases with recurrent anal fissures.

Management aims to break to constipation – fissure-constipation cycle, by use of stool softners/laxatives in response-adjusted doses and encouragement of regular evacuation habits. Fissures tend to recur in habitually constipated children.

Rectal prolapse denotes exteriorization of rectal mucosa through the anus. When this extrusion includes all layers of rectal wall, it is termed as *Procidentia.*

Etiologically, rectal prolapse is common in 1–5 years age group, with following predisposing factors: (a) severe malnutrition, (b) acute/persistent diarrhea, (c) constipation, (d) meningocele, (e) pertussis, (f) chronic inflammatory bowel disorders, e.g. ulcerative colitis, and (g) postoperative cases of anorectal malformations.

Clinically, rectal prolapse may be painless or painful and reducible or non-reducible. Severe cases may develop congestion, edema and ulceration of exteriorized portion.

Management includes: (a) manual reduction of protruding mass, facilitated by warm compresses, (b) treatment of primary cause, (c) ensuring adequate nutrition, and (d) surgical correction in severe cases or procidentia.

Perianal abscesses are relatively common and self-limiting in infancy, probably caused by extension of infection from underlying crypts. However, these

abscesses in children beyond 2 years are usually associated with a significant predisposing illness, e.g. Crohn's disease, Hirschsprung disease or immunodeficiency disorders.

Most perianal abscesses are polymicrobial in etiology, commonest being *E.coli, Staph. aureus* and anaerobes.

Clinically, these children present with variable severity of fever, rectal pain, painful defecation and signs of perianal cellulitis. Many cases in infancy may be completely asymptomatic.

Treatment: Perianal abscesses in infants are usually self-limiting, though abscess drainage and/or fistulotomy is required in selected cases. Older children with predisposing factors require more aggressive treatment with antibiotics, excision/drainage and treatment of underlying cause.

14.16 PANCREATIC DISORDERS

Embryologically, pancreas develops as an evagination from primitive duodenum and drains in it via a main duct, i.e. *duct of Wirsung,* though an accessory duct, i.e. *duct of Santorini* is also present in 15% population.

Physiologically, pancreas has endocrinal function to secrete insulin from *islets of Langerhans* as well as exocrine function to secrete over twenty digestive and absorptive enzymes, e.g. lipase (for fat), trypsin and chymotrypsin (for proteins). Clinical features of malabsorption appear only after ~90% of pancreatic activity is lost. Pancreatic enzymes, specially lipase, are low in newborns, leading to poor fat tolerance in them.

Exocrinal pancreatic insufficiency is commonly seen in cystic fibrosis, though other causes include pancreatitis, severe malnutrition, Schwachman syndrome (neutropenia, failure to thrive and malabsorption) and inherited enzyme deficiencies.

Acute pancreatitis in children is usually caused by: (a) viral infections, e.g. mumps, (b) blunt abdominal trauma, or (c) drugs, e.g. antiretrovirals agents.

Clinically, it presents with acute epigastric pain, persistent vomiting, fever and significant fluid-electrolyte imbalance. *Acute hemorrhagic pancreatitis*, seen in adults with shock, is rare in children.

Diagnosis depends on the presence of any two of the following three findings: (a) abdominal pain compatible with pancreatic origin, (b) elevation of serum amylase/lipase >3 times of the upper normal limit, and (c) imaging studies suggestive of acute pancreatitis. Presence of organ failure, e.g. respiratory distress, shock, DIC and renal failure suggests moderate to severe disease.

Management is mainly conservative with nasogastric suction, fluid and electrolyte correction and pain relief with NSAIDs or paracetamol. Antibiotics are not required except in acute infected necrotizing pancreatitis and surgery is rarely indicated in acute phase, except to drain an abscess. Uncomplicated cases usually recover in 3–4 days.

However, many children are prone for recurrent pancreatitis, i.e. more than two episodes with at least one-month symptom-free interval.

Pseudocyst of pancreas is a sequel of acute pancreatitis, though uncommon in children. These cases present with palpable abdominal mass with/without ascites or jaundice, after 2–4 weeks of acute illness. Diagnosed on USG/CT, no treatment is necessary for small lesions, while large pseudocysts need percutaneous or laparoscopic drainage.

Chronic or recurrent pancreatitis in children may be *idiopathic,* e.g. juvenile tropical pancreatitis or *secondary* to autoimmune, hereditary (cystic fibrosis) or metabolic disorders or congenital malformations. Many of them present with fat malabsorption (exocrine dysfunction) or diabetes mellitus (endocrinal dysfunction).

Diagnosis of chronic pancreatitis requires *suggestive imaging finding,* e.g. altered echotexture of pancreas with/without calcifications and dilatation, strictures or calculi of the pancreatic duct, along with one of the following three criteria: (a) abdominal pain consistent with pancreatic origin, (b) evidence of exocrine pancreatic insufficiency, or (c) evidence of endocrinal pancreatic insufficiency.

Etiological evaluation also includes sweat chloride test, USG/CT, magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP).

Treatment depends on the cause, along with supportive therapy, oral pancreatic enzyme replacement and management of diabetes. Endoscopic treatment may be required for pseudocysts, ductal lesions and calculi.

Juvenile tropical pancreatitis is the commonest cause of chronic pancreatitis in children or adolescents of developing countries. In India, maximum cases have been reported from Kerala, though the incidence has declined in recent years.

Etiology is uncertain, probably related to pancreatic injury in malnutrition, trace-element deficiencies, e.g. Vitamin A, C, zinc, copper, manganese, selenium; or consumption of an unidentified substance in *cassava tapioca*-staple diet in endemic areas.

Clinically, these cases present with recurrent abdominal pain in childhood and pancreatic calculi and/or diabetes mellitus in adolescence. While persistent steatorrhea is uncommon due to poor dietary intake in affected population, fat intolerance is obvious on excessive intake. On examination, these children are typically emaciated with distended abdomen, parotid enlargement and sometimes, a cyanotic hue on lips.

Diagnosis is often missed as functional abdominal pain, till pancreatic calculi are visible on abdominal X-rays. Confirmation requires USG/CT/MRI and ERCP (dilated pancreatic duct).

Treatment is largely supportive including avoidance of fat in diet, oral pancreatic enzyme replacement and management of Diabetes. Endoscopic treatment may be required for ductal lesions and calculi.

14.17 DISORDERS OF GALLBLADDER

Embryologically, biliary tree develops from a ventral evagination of the primitive foregut into septum transversus and includes biliary canaliculi, and ductules, hepatic ducts, gallbladder and common bile duct, which ultimately opens at ampulla of Vater in duodenum along with pancreatic duct.

Physiologically, biliary tree transports the hepatic products, i.e. bile to the gut, while gallbladder acts as a reservoir.

Obstructive jaundice is the pathognomonic manifestation of biliary tract disorders (Ch 15.3). While neonatal cholestatic syndromes have been discussed elsewhere (Ch 12.14), other important biliary tree disorders in older children are as follows:

Acute hydrops is the sudden distension of gallbladder in absence of stones, congenital malformations and bacterial infection. Round worms, prolonged fasting, total parenteral nutrition and enteric fever are common causes of acute hydrops, presenting as right upper quadrant pain, tenderness (*Murphy sign*) and palpable mass, with or without fever, vomiting and jaundice.

USG reveals distended echo-free gallbladder without dilatation of biliary tree and most cases may be managed conservatively.

Acute acalculous cholecystitis is uncommon in children, seen as a part of generalized septicemia due to any cause, (e.g. enteric fever) or following blunt abdominal trauma. While clinical features are usually indistinguishable from acute hydrops, presence of high fever with chills, primary septicemia and leukocytosis indicate infective etiology and need for surgical exploration. Diagnosis is usually confirmed on laparotomy and cholecystectomy is often needed.

Cholelithiasis (gallstones): Gallstones in children are commonly *pigment stones* (>70–80%), seen in cases with: (a) hemolytic anemia, (b) chronic liver disease, e.g. Wilson disease, (c) history of neonatal cholestasis, and (d) prolonged total parenteral nutrition. *Cholesterol stones* are rare in children, seen in adolescent obese girls with idiopathic biliary dyskinesia.

Clinically, these cases may be asymptomatic or present with recurrent upper right quadrant abdominal pain and/or intolerance to fatty foods.

Diagnosis is confirmed on USG and cholecystectomy is the treatment of choice along with operative cholangiography to exclude other calculi in common bile duct. Presence of gallstones in the bile duct is often associated with acute biliary colic and obstructive jaundice, best diagnosed on MRCP or ERCP. Hemolytic anemia should be excluded in all cases.

Choledochal cysts, i.e. *congenital cystic dilatations of common bile duct*, present with recurrent cholestatic jaundice, progressive biliary obstruction or biliary cirrhosis. A diverticula of the common bile duct or dilatation of intra-duodenal portion of common duct is termed as *choledochocele*. Choledochal cysts are classified from Type 1–5 as per *Todani classification*, the type 5 termed as *Caroli disease* with intrahepatic cystic lesions. *Caroli syndrome* refers to caroli disease with congenital hepatic fibrosis.

Clinically, most cases present in childhood with a triad of-abdominal pain, right quadrant mass and cholestatic jaundice. Young infants and children may also present with biliary peritonitis due to spontaneous bile duct perforation.

Diagnosis rests of USG, though MRCP is advised before surgery to delineate the lesions.

Treatment involves primary excision of cyst with Roux-en-Y choledochojejunostomy, advocated even in asymptomatic cases due to risk of malignant transformation in later life.

14.18 DISORDERS OF PERITONEUM

Peritoneal disorders may be inflammatory (peritonitis) or non-inflammatory (ascites).

Acute peritonitis is either *spontaneous* or *secondary* **(Table 14.26)**. While spontaneous peritonitis denotes peritoneal infection via hematogenous/lymphatic route from a source outside the abdomen, secondary peritonitis denotes extension of infection from an abdominal viscera.

Etiology: Spontaneous bacterial peritonitis (SBP) is usually caused by a single pathogen, e.g. *S. pneumoniae, S. fecalis, Staph. aureus* or gram negative organisms, e.g. *E.coli* and *Kleb. pneumoniae*. secondary peritonitis is usually *polymicrobial*.

TABLE 14.26: Causes of peritonitis

- **Primary (spontaneous)**
  - Generalized septicemia
  - Infected ascites, e.g. nephrotic syndrome, cirrhosis
- **Secondary (extended infection or perforation)**
  - *Intestines:* Obstruction, appendicitis, diverticulitis
  - Umbilical sepsis in newborns
  - *Liver:* Hydatid cyst, pyemic/amebic abscess
  - *Biliary:* Cholecystitis, worms, gallstones
  - Acute pancreatitis
  - *Lymph node:* Tuberculosis
  - *Foreign body:* VP shunt
  - Traumatic/post-surgical infection

SBP is an important complication of nephrotic syndrome, usually caused by capsulated organisms due to complement deficiency. On the other hand, peritonitis associated with ventriculoperitoneal shunt is usually caused by *Staph. epidermidis*, *Staph. aureus* and *Candida albicans.*

Clinically, acute bacterial peritonitis presents with high fever, diffuse abdominal pain and vomiting. On examination, these cases appear toxic with following typical features:

- *Silent abdomen*, i.e. restricted breathing movements to avoid pain,
- *Rebound abdominal tenderness*, guarding and/or board-like rigidity,
- *Diminished or absent bowel sounds*.

Free fluid may be present and circulatory shock is common. Loss of liver dullness indicates pneumoperitoneum. Presence of ascites in nephrotic syndrome or cirrhosis with pain or fever favors diagnosis of spontaneous peritonitis.

Diagnosis must be suspected clinically, supported by polymorphonuclear leukocytosis and abdominal skiagram showing generalized haziness with sparse bowel gas shadows. Presence of free air under diaphragm (perforation) or multiple air-fluid levels (obstruction) indicate secondary peritonitis. USG with abdominocentesis is indicated in all cases to confirm the presence of fluid and differentiate ascites from peritonitis (proteins >2.5 gm/dl, cell count >250 cells/mm^3 with polymorphonuclear predominance), as well as for microbiological studies.

Management is largely conservative and includes:

- *IV antibiotic therapy*, which must be started immediately and empirically with Cefotaxime and an aminoglycoside, modified after culture reports. Additional IV metronidazole is recommended in secondary peritonitis. Therapy should be continued for 7–10 days.
- *Supportive measures* include no oral feeds, nasogastric decompression, fluid and electrolyte correction, parenteral nutrition and treatment of shock with volume expanders and vasopressors.
- *Surgical intervention* is needed only for underlying perforation or if peritoneal abscesses have developed.

Tubercular peritonitis, common in Indian children, results from spread of infection from regional lymph nodes and presents as a subacute peritonitis or ascites. Despite larger fluid collection, abdominal signs are less marked than in bacterial peritonitis and ascitic fluid is typically straw colored exudate with lymphocytic hypercellularity and cobweb formation on standing. USG/CT may reveal underlying abdominal lymphadenopathy or intestinal tuberculosis. Treatment includes specific anti-tubercular therapy with or without steroids (Ch 10.13, 14.12).

Fig. 14.21: Ascites.

Ascites denotes accumulation of any fluid within peritoneal cavity **(Fig. 14.21)**. However, this term is generally reserved for serous and sterile fluid collections, while exudative ascites is referred as peritonitis.

Etiology: Congenital malformations of thoracic duct or hydrops fetalis are common causes of ascites in newborns. In older children, it may be mechanical (altered hydrostatic:oncotic pressure balance), inflammatory or traumatic in origin **(Table 14.27)**.

TABLE 14.27: Causes of ascites in children

Transudative ascites

- ↓ ***Plasma oncotic pressure*** *(hypoproteinemia)*
  - *Hepatic:* Cirrhosis, acute liver failure
  - *Renal:* Nephrotic syndrome
  - *Nutritional:* PEM
- ***Hydrostatic pressure***
  - *Cardiac:* CCF, pericardial effusion
  - *Vascular:* Budd-Chiari syndrome
  - *Hepatic:* Congenital hepatic fibrosis
  - Portal hypertension
- ***Miscellaneous***
  - VP shunt
  - Peritoneal dialysis
  - Connective tissue disorders (Serositis)

Exudative ascites *(peritonitis)*

- ***Primary***
  - Tubercular peritonitis
  - Spontaneous bacterial peritonitis
- ***Secondary***
  - Intestinal perforation
  - Pancreatitis or ruptured pancreatic duct
  - Biliary tree anomalies/injury (Biliary ascites)
  - Urinary tract anomalies/injury (Urinary ascites)

Hemorrhagic ascites

- Malignancies
- Traumatic (penetrating or blunt abdominal trauma)
- Splenic rupture

Chylous ascites

- Thoracic duct anomalies or injuries

Diagnosis: Abdominal distension is the hallmark of ascites, though other causes, e.g. gaseous distension, organomegaly or *pot belly* must be excluded. Depending on the amount of fluid collection, various clinical signs include:

- *Flank fullness* and *Puddle sign* (<50 ml fluid)
- *Shifting dullness/horse-shoe dullness* for moderate ascites, and
- *Fluid thrill* in large ascites.

Investigations: USG is the best tool to detect minimal ascites and for diagnostic paracentesis. Important characteristics of ascitic fluid include:

- ***Color:*** Watery (transudate), straw-colored (tubercular), hazy or pus (bacterial peritonitis), bloody (traumatic/hemorrhagic), milky-white (chyle), greenish (biliary), tea-colored (pancreatitis).
- ***Proteins:*** Transudative (<2.5 gm/dl) or exudative (>2.5 gm/dl). As ascitic fluid hypoproteinemia is common in generalized hypoproteinemic states including SAM. A more informative test is to calculate serum: ascitic fluid albumin ratio. A ratio of >1.1:1 suggests portal hypertension.
- ***Leukocyte count*** of >500 cells/mm^3 indicates exudative pathology, specially if >50% of them are polymorphs.

Other tests, e.g. bacterial and tubercular culture (peritonitis), triglycerides (chylous ascites), amylase (pancreatic etiology), LDH (spontaneous bacterial peritonitis) are also useful in diagnosis.

Management: Apart from treatment for primary cause, general management of ascites includes:

- *Bed rest* to decrease the discomfort as well as reduce renin-angiotensin activity, which is higher in upright position.
- *Dietary restriction* of sodium, though fluid restriction is not necessary unless serum sodium is <120 mEq/L.
- *Diuretics,* preferably potassium-sparing ones, e.g. spirolactone may be used in severe cases with caution to avoid hypovolemia.
- *Therapeutic abdominocentesis* carries the risk of infection in sterile ascites and recommended only in cases with marked discomfort and respiratory distress. Infected peritoneal fluid must be treated as peritonitis, discussed earlier.

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CHAPTER

15

Disorders of Hepatobiliary System

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15.1 BASIC CONSIDERATIONS

Embryologically, liver develops from two sources: (a) *Biliary tree and hepatocytes* from ventral evagination of the primitive foregut (endoderm) into mesodermal septum transversus, and (b) *Kupffer cells and supporting elements*, e.g. endothelial cells, fibrous tissue and blood vessels from the mesoderm itself.

Anatomically, basic architecture of liver parenchyma may be broadly divided into two elements: (a) *hepatic lobules*, i.e. pentad arrangement of hepatocytes with a central vein and surrounding sinusoids, and (b) *portal triads* containing portal venules, hepatic arterioles and biliary canaliculi. A thick limiting plate of connective tissue separates hepatic lobules and portal triads from each other.

The biliary system includes biliary canaliculi, and ductules, hepatic ducts, gallbladder and common bile duct, which ultimately opens at ampulla of Vater in duodenum along with pancreatic duct.

Vascular supply: Liver is a highly vascular structure with dual blood supply—via *portal circulation* (75%) and via hepatic artery of *systemic circulation* (25%). *Portal vein* is formed by the fusion of splenic and superior mesenteric veins and carries most of the gastrointestinal blood flow to liver for metabolism of absorbed nutrients. It also supplies about half of the oxygen demand of liver, while remaining half is supplied by hepatic arteries. Branches of portal vein and hepatic artery are present in portal triad along with bile ducts, from where they traverse through limiting plates to enter venous sinusoids surrounding hepatocytes and drain into central hepatic vein. Liver does not have a capillary system (but sinusoids).

Physiologically liver plays a vital role in—(a) synthesis, storage and metabolism of various nutrients, (b) detoxification of metabolites, drugs and hormones and (c) excretion of certain substances in gut **(Table 15.1)**. Liver is also a major site for hematopoiesis in fetal life.

Laboratory evaluation in liver disease aims to confirm the diagnosis of liver disease as well as to assess its course. Important components of hepatic evaluation include:

TABLE 15.1: Physiological functions of liver

- **Bilirubin metabolism** (conjugation/excretion)
- **Carbohydrate metabolism**
  - Glycogen storage (Glucose > Glycogen)
  - Lipogenesis (Glucose > Lipids)
  - Neoglucogenesis (Amino acids > Glucose)
  - Glycogenolysis (Glycogen > Glucose)
- **Protein metabolism**
  - Protein synthesis (Amino acids > Proteins)*
  - De-amination (Amino acids > Ammonia > Urea)
- **Lipid metabolism**
  - Formation and utilization of fatty acids
  - Synthesis and esterification of cholesterol
  - Synthesis of phospholipids and triglycerides
  - Formation and conjugation of bile salts
- **Hormone metabolism**
  - Detoxification of steroids
  - Degradation of enzymatic proteins
- **Drug metabolism and excretion**
- **Reticulo-endothelial function**
  - Phagocytosis via Kuppfer cells
  - Immunoglobulin synthesis

*e.g. albumin, clotting factors, transport-proteins, etc.

a. **Imaging procedures** for evaluation of anatomical lesions and excretory function:

- *Ultrasonography* is a baseline investigation for evaluation of hepatic size, focal lesions, e.g. abscesses, portal hypertension and biliary tract abnormalities. CT/MRI is more useful to delineate small focal lesions and tumors. MR cholangiography is valuable in assessment of pancreatico-biliary disorders.
- *Radionucleotide liver scan* is used for diagnosis of focal lesions (Tc^{99} sulfur colloid scan) or assessment of excretory functions (Tc^{99m} iminodiacetic acid-IMIDA scan).
- *Other* imaging procedures, e.g. angiography, and endoscopic retrograde cholangiography (ERCP) are used in selected cases.

b. **Liver function tests (LFTs):** As the liver has large functional reserve, biochemical abnormalities usually

precede clinical manifestations. Important liver function tests include:

- *Tests for metabolic or synthetic dysfunction*
  - Serum bilirubin (unconjugated fraction)
  - Prothrombin time and INR*
  - Serum proteins, specially albumin.
  - Serum ammonia (in acute cases)
- *Tests for hepatocellular injury***
  - Serum aspartate aminotransaminase (AST/SGOT)
  - Serum alanine aminotransferase (ALT/SGPT)
- *Tests for cholestasis*
  - Serum alkaline phosphatise (ALP)
  - Serum gamma-glutamyl transpeptidase (GGT)***
  - Serum bilirubin (conjugated fraction)
- *Tests for immune dysfunction*
  - Altered gammaglobulin levels
  - Presence of antinuclear antibodies

*INR (International Normalized ratio) is the ratio of patient's prothrombtin time compared to control value, raised to the power international sensitivity index.

**AST and ALT are intracellular enzymes, released on cellular injury. ALT is mainly present in liver cells, while AST is also present in muscles and some other tissues. Hence, elevated ALT is more reliable indicator of hepatocellular injury than AST.

***GGT is more reliable indicator of cholestatic disease than ALP, which is also high in growing children due to bone isoenzyme fraction. GGT is normally high in newborns and infants < 6–9 months.

c. **Liver biopsy** is *indicated* in—(a) chronic liver disease or cirrhosis, (b) suspected metabolic or infiltrative disease, (c) unexplained, persistent icterus or abnormal liver function tests. However, it is *contraindicated* in—(i) acute liver failure, (ii) bleeding disorders, (iii) congestive hepatomegaly or vascular malformations of liver, and iv) suspected hydatid disease. Normal prothrombin time is an essential prerequisite for liver biopsy. (Ch 32.6)

15.2 HEPATOMEGALY

Liver is normally palpable up to 2 cm in first two years of life, though *Riedel lobe* may be palpable even in older children. A palpable liver does not necessarily mean hepatomegaly and may be *pushed-down* by thoracic pathology, e.g. pneumothorax *or visceroptosis* in cases of ligamental laxity, e.g. rickets. Hence, it is always preferable to record *liver span* by localizing the upper border (by percussion) and lower border (by palpation).

Normal liver span is ~5 cm in newborns and ~7 cm in older children. A liver span of >8 cm in childhood is abnormal.

Etiology: Hepatomegaly may be-(a) infective, (b) metabolic, (c) hematologic, (d) infiltrative, or (e) congestive in origin, apart from rare congenital malformations **(Table 15.2)**.

TABLE 15.2: Cause of hepatomegaly

- **Infective Hepatomegaly**
  - *Viral:* Hepatitis A–E, HIV, EBV
  - *Bacteria:* Typhoid, sepsis, abscess, tuberculosis
  - *Spirochetal:* Leptospirosis
  - *Protozoa:* Amoebic hepatitis
  - *Parasitic:* Malaria, kala-azar
  - Intrauterine infections
- **Autoimmune hepatitis**
- **Congestive hepatomegaly**
  - *Cardiac:* CCF, pericarditis
  - *Pre-cardiac:* Budd-Chiari syndrome
- **Compensatory hepatomegaly (↑ erythropoiesis)**
  - Hemolytic anemia
  - Nutritional anemia
- **Metabolic/storage disorders**
  - *Carbohydrates:* Glycogen storage disorders
  - *Fat:* Gaucher/Niemann-Pick disease
  - *Mineral:* Indian childhood cirrhosis, Wilson disease
  - *Protein:* Tyrosinemia, Reye syndrome
- **Cholestatic syndromes**
- **Infiltrative hepatomegaly**
  - Leukemia, lymphoma
  - Hepatic tumors (primary/metastatic)
  - Histiocytosis
- **Congenital cysts, malformations and CHF**
- **Miscellaneous**
  - Physiological (<2 years)
  - *Displaced liver:* Visceroptosis, pneumothorax
  - Drug-induced Hepatitis

CHF: Congenital hepatic fibrosis

D/D between various causes of hepatomegaly **(Table 15.3)** depends on:

- *Characteristics*, e.g. (i) size, (ii) consistency, (iii) surface, (iv) margins, (v) tenderness, and (vi) vascularity, e.g. bruit or pulsations
- *Age:* Hepatomegaly in newborns and young infants usually indicate intrauterine infections, septicemia, cholestatic syndromes and metabolic disorders, while hemolytic anemia and congestive hepatomegaly is more common in older infants and toddlers. Viral hepatitis and other infective causes predominate in school children.
- *Co-existing splenomegaly* usually indicates portal hypertension, hemolytic anemia, chronic infections, metabolic disorders or infiltrative disorders, e.g. leukemia. Isolated hepatomegaly is mainly infective (viral hepatitis, abscess) or congestive in origin (cardiac failure).
- *Associated findings*, e.g. jaundice (viral hepatitis), pallor (hemolytic anemia, leukemia), lymphadenopathy (malignancy), ascites (chronic liver disease), etc. provide vital diagnostic clues in hepatomegaly.

TABLE 15.3: D/D Broad causes of hepatomegaly

	Infective	*Metabolic*	*Hematological*	*Congestive*	*Infiltrative*
Liver characteristics					
Size	+/++	++++	++	++	++/+++
Consistency	Firm	Firm	Firm	Soft/firm	Hard/firm
Surface	Smooth/nodular	Smooth/nodular	Smooth	Smooth	Nodular/smooth
Margins*	Sharp	Rounded	Well-defined	Sharp	Well-defined
Tenderness	+	–	–	++	–
Bruit/pulsation	–	–	–	+	–
Associated findings					
Spleen	+/–	++	++++	–/+	+/++
Jaundice	+	–/+	–/+	–	+/–
Pallor	+/–	–/+	++++	–	++
Lymphadenopathy	+/–	–/+	–	–	++
Ascites	+/–	–/+	–	–/+	++
Other	Fever	CNS signs/MR	H/o transfusions	CVS disease	Primary tumor

*finding may change over time

15.3 JAUNDICE

Jaundice (Icterus) is a clinical diagnosis with *yellowish discoloration of sclera, mucus membranes and skin*, due to elevated serum bilirubin levels. Normal serum bilirubin levels are 0.3 –0.8 mg/dl with predominant unconjugated fraction (unconjugated:conjugated ratio > 8:1). However, icterus is clinically visible, only when serum bilirubin levels exceeds 2.0 mg/dl.

Normal bilirubin metabolism and neonatal jaundice is discussed in Chapter 12.13. Present section mainly pertains to post-neonatal jaundice.

Etiology: Common causes of post-neonatal jaundice may be divided into—(a) *hemolytic jaundice* due to increased bilirubin production, (b) *hepatic jaundice* due to impaired bilirubin metabolism, and (c) *obstructive* or *cholestatic jaundice* due to inadequate bilirubin excretion **(Table 15.4)**.

Diagnostic evaluation: Clinical differentiation between three broad groups—hemolytic, hepatic and obstructive jaundice, is the first step in evaluation of jaundice **(Table 15.5)**, followed by relevant laboratory studies for specific etiology. Important diagnostic clues include:

- *Course:* Hepatitis A is the commonest cause of short duration, self-limiting icterus (<2–3 weeks) in Indian children, while prolonged icterus indicates chronic liver disease or congenital hemolytic anemia. Recurrent jaundice is common in chronic liver diseases or choledochal cysts.
- *Relevant history* related to adverse environmental factors (infective hepatitis), similar family history (hemolytic anemia, metabolic disorders) or previous treatment (drug-induced).

TABLE 15.4: Causes of jaundice (Post-neonatal)

Hemolytic jaundice
- *Congenital:* Hereditary spherocytosis, thalassemia
- *Drug/toxins:* Quinine (in G6PD deficiency)
- *Acquired:* Malaria, polycythemia, transfusions
- *Micro-angiopathic:* Hemolytic-uremic syndrome

Hepatic jaundice
- *Infective:* Viral hepatitis, leptospirosis, malaria,
- *Drug/toxins:* Isoniazid, rifampicin, valproate
- *Chronic liver disease:* Chronic active hepatitis, cirrhosis
- *Metabolic:* Wilson disease
- *Familial:* Crigler-Najjar syndrome, Gilbert syndrome

Obstructive jaundice
- Neonatal hepatitis
- Intrahepatic biliary atresia
- *Extrahepatic causes:*
  - Biliary tree-extrahepatic biliary atresia
  - Gallbladder-gallstones, choledochal cyst
  - Porta hepatis-tubercular nodes, portal fibrosis
  - Ampulla of Vater-worms, pyloric stenosis
- *Inherited:* Dubin-Johnson/Rotor syndrome*

*Conjugated jaundice, but not due to obstructive etiology

- *Itching and clay-colored stools* strongly indicate obstructive jaundice, though these features are not uncommon in recover phase of infective hepatitis.
- *Coexisting splenomegaly* with pallor indicates hemolysis—congenital or acquired (malaria, sepsis).
- *Signs of metabolic liver dysfunction*, e.g. edema, ascites, steatorrhea, etc. indicates hepatic jaundice.
- *Liver function tests* differentiate between hemolytic, hepatic and obstructive jaundice, though further investigations are needed to pinpoint exact etiology.

TABLE 15.5: D/D Broad types of jaundice

Features	*Hemolytic*	*Hepatic*	*Obstructive*
Age of onset	Infancy[1]	Any age[4]	Infancy[7]
Duration of icterus	Persistent[2]	Acute[5]	Acute, recurrent[8]
Family history	Present	Absent[6]	Absent[9]
Past history	Drugs[3], Transfusions	Viral infections	Drugs, Hemolytic anemia[10]
Itching	Absent	±	Marked
Stool color	Normal	Normal	Clay colored
Urine color	Normal	Dark	Dark
Splenomegaly	Marked[1]	± Mild	± Mild
Anemia	Marked	±	±
Serum bilirubin	Unconjugated	Mixed	Conjugated
SGOT/PT	Normal	Elevated	Normal
SGGT	Normal	Normal/Elevated	Elevated
Serum alkaline PO_4	Normal	Normal/Elevated	Elevated
Urine urobilinogen	++	+	Absent

[1] except G6PD deficiency, [2] or recurrent (G6PD def./sickle cell disease), [3] in G6PD deficiency, [4] HAV after 3–5 years, Wilson disease after 5 years, [5] persistent in chronic liver disease, [6] present in Wilson disease and other metabolic causes, [7] or in late childhood (gallstones), [8] recurrent in choledochal cyst, gallstones, [9] except in hemolytic gallstones, [10] due to gallstones

15.4 VIRAL HEPATITIS

Acute hepatitis is a clinical syndrome of heterogeneous etiology **(Table 15.6)**, characterized by abrupt onset of clinical jaundice and/or laboratory evidence of hepatic dysfunction, e.g. elevation of bilirubin and liver enzymes. Most of these cases are due to infection by hepatotropic viruses, discussed in this chapter.

Viral hepatitis refers to *primary infection of the liver due to heterogeneous group of specific hepatotropic viruses, designated as A-G*. Hepatitis due to other viruses, e.g. CMV, HSV, EBV, etc. is generally excluded from this terminology.

While liver pathology in all hepatotropic viral infections is nearly similar during acute stage (centrilolobular necrosis and periportal infiltration without destruction of normal architecture); route of infection, severity/duration of disease and later course differs significantly **(Table 15.7)**.

TABLE 15.6: Common causes of acute hepatitis

- **Infective:**
  - *Hepatotropic viruses:* HAV, HBV, HCV, HEV
  - *Other viruses:* CMV, EBV, dengue
  - *Bacterial:* Septicemia, enteric fever, leptospirosis
  - *Others:* Amoebiasis, malaria, brucellosis
- **Drugs and Toxins:**
  - *Drug-induced:* INH, Rifampicin, Valproate
  - *Poisoning:* Paracetamol, pesticides
- **Metabolic:**
  - Reye syndrome
  - *Others:* Wilson disease*
- **Others:**
  - Autoimmune hepatitis*
  - Budd-Chiari syndrome
  - Acute cholestatic syndromes

*Acute manifestation of chronic disease

Hepatitis A (HAV) is the commonest cause of viral hepatitis in children, though clinical disease is mild, self-limiting and generally benign. Complications, e.g. acute liver failure or chronic liver disease are extremely rare.

Epidemiology: HAV is excreted in stools of a clinical or subclinical case and transmitted via *feco-oral route* by ingestion of contaminated water/food.

High-risk factors: Focal outbreaks are common in summer and rainy season, specially in unsanitary slums with contaminated water supply. Though no age is immune, HAV is rare <2 years due to less risk of exposure, with highest risk in school-children.

Clinical manifestations: Incubation period varies from 15 to 45 days. HAV infection is relatively mild in children than in adults and presents as anicteric or icteric disease.

Anicteric hepatitis accounts for >80% of HAV infections, presenting as low-grade fever, vomiting, diarrhea, mild tender hepatomegaly and borderline liver function tests abnormalities for 1–2 weeks.

Icteric hepatitis indicates more severe hepatic injury, with appearance of jaundice after few days of prodromal symptoms and more moderate hepatomegaly. Symptoms tend to improve once the jaundice sets in, which lasts for 2–3 weeks. Mild pruritis is common, specially in recovery phase.

TABLE 15.7: Common hepatotropic viral infections

Feature	*HAV*	*HBV*	*HCV*	*HEV*
Incubation (days)	15–50	50–150	15–180	20–60
Agent (virus)	RNA	DNA	RNA	RNA
Route of infection	Ent	Pnt/Prnt	Prnt	Ent
Extra-hepatic signs	Nil	+	+	Nil
Complications	Rare	Common	Common	Rare
Treatment	NS	NTdA	DAAs	NS

Ent: Enteral; **Prnt:** Pareteral; **Pnt:** Perinatal; **NS:** Non-specific; **NTdA:** Nucleos(t)ide analogues; **DAA:** Direct acting antivirals

Diagnosis may be confirmed by presence of anti-HAV IgM antibodies in second week. Elevated anti-HAV IgG has no diagnostic value for acute disease, merely indicating past infection or vaccination.

Liver function tests are indicated as base-line parameter, though serial testing is unnecessary in clinically improving case. Serum alkaline phosphatase may be elevated in recovery phase due to transient cholestasis.

Presence of bile salts and pigments in urine is a simple screening method in hepatitis**,** tested by *Hay's sulfur test* and *Fouchet test* respectively (Ch 21.2).

D/D includes other causes of acute hepatitis **(Table 15.6)**, closest being HEV and drug-induced hepatitis.

Treatment: HAV hepatitis is self-limiting, without specific therapy except nutritious high carbohydrate diet and avoidance of excessive fat. Complications, e.g. fulminant hepatic failure are extremely rare, except in cases with pre-existing liver disease (<1%). Some cases may develop prolonged *cholestasis* waxing and waning course but with eventually complete recovery.

Prevention of HAV depends on:

- *Public health measures*, i.e. improvement of sanitation and potable water supply. Patients are contagious from 2 weeks before to about a week after the onset of jaundice.
- *Personal protection*, i.e. use of boiled or UV exposed water, specially during epidemics,
- *Active immunization* with either two doses of inactivated HAV vaccine in second year of life at 6–18 months interval *or* a single dose of Live HAV vaccine at 12 months of age. While not yet included in National Immunization schedule, IAP recommends HAV immunization to *all* children, specially those with—(a) chronic liver disease, or (b) institutionalized care, e.g. orphanages.

  Catch-up immunization is recommended till 10 years, while pre-vaccination screening for HAV antibodies is advised before vaccination in older children (>10 years) due to substantial chance of natural infection and immunity by this age.
- *Post-exposure prophylaxis* is indicated in household contacts within 10 days of exposure, preferably with initiation of HAV vaccination. Immunoglobulins (IM 0.02–0.06 ml/Kg) may be used in infants or immunocompromised children.

Hepatitis B (HBV), though less common than HAV, is an important health problem due to higher risk of late complications, e.g. chronic liver disease, cirrhosis and hepatocellular carcinoma. India is in the intermediate risk zone of HBV prevalence, with chronic carrier rate of ~3–4%.

Epidemiology: HBV, also referred as *Dane particle*, is a DNA virus containing many antigens, most important being a surface antigen (*HbsAg*), a core antigen (*HbcAg*) and a non-structural antigen (*HbeAg*).

Persons with chronic HBV infection are primary reservoir of infection. Children are usually infected from mothers (*perinatal/vertical transmission*), though *horizontal transmission* via parenteral route, i.e. transfusions, accidental needle pricks, drug abuse *or* sexual contact is not uncommon.

Risk of perinatal transmission is highest when mother is both HbsAg and HbeAg positive (70–90%), than in HbeAg negative mothers (25%), if HB vaccine with/without immunoglobulins (HBIG) is not given within 24 hours.

Clinical spectrum: Perinatal HBV infections are generally asymptomatic in childhood, despite potential risk for future liver disease. A symptomatic case presents after an incubation period of 50–180 days, with:

- *Non-specific prodrome*, e.g. lethargy, anorexia and malaise
- *Icterus* in <25% cases, lasting for ~ 4 weeks,
- *Extra-hepatic manifestations* of probable immune etiology, e.g. arthralgia/arthritis, rash or papular acrodermatitis (*Gianotti-Crosti syndrome*), glomerulonephritis and aplastic anemia, for 2–3 weeks.

Unless complicated by fulminant liver failure, acute episode lasts for 4–6 weeks.

Complications: HBV infection is associated with considerable early and late morbidity, including (a) acute fulminant liver failure in 30%, (b) chronic liver disease, including cirrhosis in 40% and (c) hepatocellular carcinoma in <5–10%. Except acute liver failure, other complications may develop even in asymptomatic cases or carriers.

Infections acquired before 5 years of age are more likely to become chronic carriers-defined as HbsAg positivity beyond 6 months. Risk of chronic carrier state after HBV infection is >90% in perinatally infection *versus* 5% in adults infections.

Diagnosis is serological and various markers are used to define chronicity and infectivity of the infection **(Fig. 15.1)**.

HBsAg is the first serological marker to appear after infection, present in almost all infected children. Clinical significance of other seromarkers includes:

- Persistence of HBsAg indicates a carrier state or chronic infection, while its disappearance within 3–6 months indicates resolution of infection.
- Presence of HBeAg indicates high infectivity and HBeAg positive mothers are more likely to transfer infection to their baby.
- Anti-HBcAg is the most useful marker to differentiate HBV immunized *vs* infected children. While anti-HBsAg is present in both, anti-HBcAg is positive only in natural infection.
- Presence of anti HBeAg antibodies indicates lesser risk of infectivity.

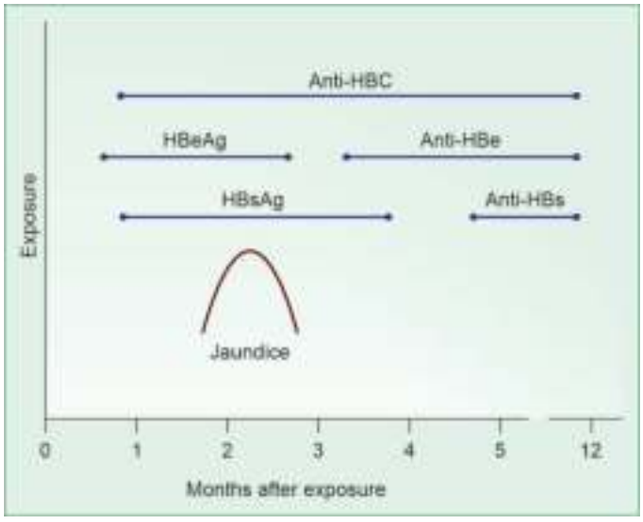

Fig. 15.1: **Natural course and sero-markers in HBV infection.**

Treatment of *acute HBV infection* is entirely supportive, including monitoring for acute hepatic failure. For treatment of chronic HBV infection, *see* Ch 15.8.

Prevention of HBV revolves around pre-and post-exposure immunization as well as strict screening of transfusion products.

- ***Infants born to HbsAg positive mothers*** should receive HB vaccine as well as HBIG (0.5 ml each, at different sites) as early as possible, preferably within 12 hours of birth, followed by HB vaccine after 1 and 6 months (or three doses as in NIS/IAP schedule). Efficacy of perinatal HBV prophylaxis is 90–95%.

  However, all children should be re-screened after 1 year for HBsAg as well as anti-HbsAg. While presence of anti-HbsAg indicates that the baby is immune, *HbsAg positivity without anti-HbsAg indicates infection without immunity and probability of progressive liver disease.* Re-vaccination is needed if both markers are negative. Breastfeeding by HBsAg positive mother, unless she is also HbeAg positive, does not increase the risk of transmission.
- ***Routine immunization*** with four doses are given in national immunization schedule at birth as stand-alone vaccine and 6, 10 and 14 weeks as pentavalent vaccine. HB vaccine is specially indicated in children with hemolytic anemia or haemophilia on multiple transfusions. Catch-up immunization in older unimmunized children or adults is indicated with three-dose 0,1, 6 months schedule.

Hepatitis C (HCV) is an emerging transfusion-related infection, which has already infected ~ 3% of world population. Exact incidence in India is not known due to limited diagnostic facilities, though HCV screening for all blood products is compulsory here since 1998.

Epidemiology: HCV infection in children is almost always transmitted via infected blood transfusion. Perinatal risk of transmission from viremic mothers is only ~ 5%.

Clinical spectrum is milder than HBV disease. Most cases are asymptomatic in early stage and clinical jaundice is seen in <25%. However, 20–50% cases progress to develop chronic liver disease, cirrhosis and hepatocellular carcinoma after many years. Chronic infection may also be associated with small vessel vasculitis and extrahepatic manifestations in adults.

Diagnosis of acute HCV disease is possible with HCV-PCR (RNA) assay after 2 months of age/exposure while serological tests turn positive only after 3–4 months of clinical illness. HCV-RNA should be repeated at ~3 years of age in children with positive serological tests to confirm chronicity of infection.

Treatment aims to clear viremia, improve liver histology and reduce the risk of chronic liver disease. Genotyping of virus is important before therapy as response may vary.

All children >3 years of age with HCV, irrespective of the genotype, must be treated with a fixed-dose combination of directly acting antivirals (DAA) including Sofosbuvir with Velpatasvir, for 12 weeks. Other DAAs or interferon/pegylated interferon therapy may be used in children with selected genotypes, including combination therapy in non-responders.

Sequential estimation of HCV-RNA is essential to monitor the therapeutic response.

Prevention: No vaccine is available against HCV and screening of donor blood remains the most effective preventive intervention.

Hepatitis D (HDV) is considered a defective RNA virus, which depends entirely on HBV for its replication. HDV infection may be either a co-infection with HBV or a super-infection, leading to acute exacerbation of chronic HBV infection. Chronic liver disease is more common, when both infection co-exist. HDV has not been isolated and diagnosis depends on detecting specific IgM antibodies.

Hepatitis E (HEV), like HAV, is a fecooral infection through contaminated water, more common in adults than children. Clinical presentation is limited to acute liver disease, which is more severe in adults, specially pregnant women. Pediatric infections are usually mild and sub-clinical. Chronic sequelae are unknown. Diagnosis rests on presence of anti-HEV IgM antibodies and treatment is symptomatic.

Hepatitis G (HGV): Advances in the molecular technology lead to identification of two newer hepatic viruses-hepatitis GB virus (HGBV-C) and hepatitis G virus (HGV). Present evidence suggests that both of them are close variants of same species, transmitted through blood transfusions or organ transplants. No serological test is presently available for diagnosis and clinical spectrum or management is yet to be defined.

15.5 ACUTE HEPATIC FAILURE

Acute hepatic failure (AHF) is a life-threatening event, characterized by *rapidly progressive hepatocellular dysfunction and multisystemic manifestations*, e.g. *encephalopathy, coagulopathy, hemodynamic disturbances and dyselectrolytemia*.

While acute liver failure may also develop in cases with pre-existing chronic liver disease, AHF is usually defined as:

- Biochemical evidence of liver dysfunction for < 8 weeks duration,
- Coagulopathy with INR >1.5 in patients with encephalopathy or >2.0 in those without encephalopathy, not corrected by vitamin K, and
- No evidence of chronic liver disease.

Depending on the onset and course, liver failure is classified as *fulminant* (<1 week), *acute* (1–4 weeks), *subacute* (4 weeks to 6 months) and *chronic* (>6 months).

Etiology: AHF in children is usually infective, toxic or metabolic in origin **(Table 15.8)**. Viral hepatitis, autoimmune hepatitis and metabolic disorders, e.g. Wilson disease are predominant causes of AHF in children. However, 30–40% cases are idiopathic.

Cases with pre-existing liver disease may also develop AHF due to superimposed insult lie viral, toxic or drug-induced hepatic injury.

Pathologically, AHF is characterized by massive necrosis of hepatocytes, loss of normal hepatic architecture and occasionally cholestasis, apart from features of primary disease.

Pathogenesis: Sudden and severe impairment in metabolic and excretory liver functions is the hallmark of AHF. Gastrointestinal bleeding, hypoglycemia, hypokalemia, drug therapy, abdominal paracentesis and high protein meal are common *precipitating factors* for AHF in cases with pre-existing liver disease.

TABLE 15.8: Important causes of AHF in Indian children

- **Infective (60–90%)**
  - *Viral hepatitis:* HAV, HEV, HBV, others.
  - Leptospirosis
  - Fulminant bacterial septicemia
- **Drug and toxins: (6–8%)**
  - *Drugs:* INH, rifampicin, Na valproate, anesthetics
  - *Poisoning:* Paracetamol, heavy metals
- **Metabolic**
  - Reye syndrome
  - Wilson disease
  - *Inborn errors:* Galactosemia, tyrosinemia
  - Indian childhood cirrhosis
- **Ischemic/hypoxic**
  - Circulatory shock
  - *Vascular obstruction:* Budd-Chiari syndrome
- **Malignancies** *(primary/metastatic)*

EBV: Epstein-Barr virus, **CMV:** Cytomegalovirus

Hyperammonemia due to impaired detoxification of ammonia into urea is the most important cause of hepatic encephalopathy, characterized by severe cerebral edema and intracranial hypertension.

Clinically important features of AHF include:

- *Encephalopathy* of variable severity-subtle mental changes, e.g. altered personality and abnormal sleep pattern, are earliest indicators of hepatic encephalopathy, which may rapidly progress to coma **(Table 15.9)**. However, presence of encephalopathy is not essential for diagnosis of AHF in children.
- *Progressive deep jaundice*, though highly suggestive, is also not essential, as many cases succumb before the appearance of jaundice.
- *Other signs of hepatic damage* include: (i) *fetor hepaticus*, i.e. ammonical breath odor and intractable vomiting due to hyperammonemia, (ii) bleeding tendency due to deficiencies of vitamin K dependent clotting factors, (iii) dyselectrolytemia with metabolic acidosis, (iv) ascites due to hypoproteinemia, and (v) diarrhea due to fat malabsorption
- *Hepatomegaly* may or may not be present. *Absence of hepatomegaly or rapid reduction in liver size is a bad prognostic indicator in AHF.*
- *Secondary complications* are common, e.g. fulminant infections due to impaired immunity, renal failure (acute tubular necrosis), pulmonary complications (aspiration, pulmonary edema), etc.

Laboratory investigations are needed to identify the cause as well as to monitoring progression of liver damage and include:

- *Hematological*:
  - CBC (leukocytosis, thrombocytopenia)
  - Coagulation profile, e.g. prothrombin time

TABLE 15.9: Stages of hepatic encephalopathy

Stage	*Findings*
I	• Alternate spells of lethargy and euphoria • Reversal of day-night cycle • Asterixis, i.e. flapping tremors • No EEG changes
II	• Drowsiness, confusion or agitation • Wide mood swings • Fetor hepaticus • *EEG:* Gen. slowing (with θ waves)
III	• Stupor, confused • Absent or Incoherent speech • Rigidity, hyperreflexia, extensor plantars • *EEG:* Marked abnormality (triphasic waves)
IV	• Deep coma • Decerebrate/decorticate posturing • Areflexia and flaccidity • *Response to pain:* Present **(IVA)** absent **(IVB)** • *EEG:* B/L slowing, Delta waves, EEG silence

- *Biochemical:*
  - LFT, e.g. serum bilirubin, AST/ALT, GGT/ALP
  - Serum ammonia (elevated in encephalopathy)
  - Serum proteins (reduced with altered A:G ratio)
  - Serum electrolytes, e.g. Na^+, K^+, HCO_3^-, Ca^{++}
  - Blood glucose (hypoglycemia)
  - Blood gas analysis (metabolic acidosis)
- *Microbiological*: Cultures, viral serology
- *EEG* to confirm/monitor encephalopathy
- Specific etiological investigations

Management of AHF is non-specific and aims to provide life support and prevent/treat complications till spontaneous recovery. All patients need intensive care and monitoring. Important measures include:

- ***Stabilization*** of hemodynamic status with fluid therapy, volume expanders, e.g. plasma, and vasopressor agents.
- ***Continuous monitoring*** for—(a) vital signs, (b) intake/output, (c) neurological assessment, (d) biochemical parameters, e.g. electrolytes, blood gases, blood sugar, PT/INR, LFT, (e) urine output and renal functions, and (f) sepsis.
- ***Gut sterilization*** to reduce ammonia production, produced due to breakdown of food-proteins or blood, by ammonia-producing microbial flora. Important measure to prevent it include:
  - PO Rifaximin (20–30 mg/kg/day) or Neomycin to eliminate ammonia-producing organisms
  - PO Lactulose (10–50 ml 4 hourly) to produce acidic media and reduces activity of organisms, dose must be adjusted to produce 2–4 loose motions per day.
- ***Fluid/electrolyte therapy*** is guided by intake-output record, central venous pressure monitoring and electrolyte estimation. Generally, N/2 saline in DW 10% with 15 mEq/l of potassium is used to provide 90% of total maintenance fluid requirements. However, volume and composition of IV fluids needs to be modified according to electrolyte status, specially to keep sodium levels between 145–155 mEq/l. *Hypoglycemia, hypokalemia and metabolic acidosis are very common* and need to be treated promptly.
- ***Cerebral edema*** is the major cause of mortality and needs to be treated promptly by IV Mannitol (0.5–1 g/kg/dose) or hypertonic saline, and controlled ventilation to prevent CO_2 retention. *Steroids are contraindicated*. There is some evidence that early encephalopathy may be reversed by a benzodiazepine antagonist – *Flumazenil.*
- ***Coagulopathies*** must be treated with fresh frozen plasma, platelets and IV vitamin K supplements (5–10 mg/day). Blood transfusion should be avoided, if possible. Cryoprecipitate may be used in low-fibrinogen states (<100 mg/dl). Plasmapheresis is useful to eliminate anticoagulant and fibrinolytic products, produced during hepatic injury.
- ***Esophageal variceal bleeding*** may require endoscopic sclerotherapy or ligation in emergency, though IV Octreotide (1–10 µg/kg 12 hourly) may be useful, if endoscopy is not possible. Antacids or proton pump inhibitors may also benefit in GIT bleeding.
- ***Treatment of other complications***, e.g. ascites, renal failure (dialysis) and infections. Empirical antibiotic therapy, though controversial, is preferable in all cases, which must be modified after cultures. *N-acetyl cysteine*-A glutathione precursor (IV infusion 100 mg/kg/d) may or may not be useful even in non-acetaminophen induced AHF, due to anti-inflammatory, antioxidant, inotropic, and vasodilating effects.
- ***Removal of toxic metabolites*** by activated charcoal, plasmapheresis or exchange transfusion may be attempted in non-responsive cases.
- ***Liver transplantation***, is the final option in refractory cases, with success rate of 60–80%.

Prognosis: Overall mortality in AHF is very high (70%), but still better in children than in adults. Bad prognostic factors include—(a) rapid onset of encephalopathy within 7 days of icterus, (b) prothrombin time >50 seconds, (c) serum bilirubin >17.5 mg/dl, (d) stage IV coma, and (e) multi-organ failure.

15.6 LIVER ABSCESS

Pyogenic liver abscesses are not uncommon in children, Solitary liver abscesses in the right lobe are more common than multiple abscesses or solitary left lobe abscesses.

Etiologically, liver abscesses usually develop as a part of generalized sepsis, as ascending infection from gastrointestinal disease or localized lesions after intra-abdominal infection, trauma or surgery.

Most common pathogenic organisms include *Staphylococcus aureus, Streptococcus* spp., *Escherichia coli, Salmonella,* and anaerobic organisms. *Entamoeba histolytica* is an important cause of liver abscess in India, though more common in adults.

Clinically these children present with fever, chills, vomiting and abdominal pain in right hypochondrium with tender hepatomegaly. Jaundice is uncommon.

Complications include spontaneous rupture in peritoneum, pericardium or pleural space or metastatic abscesses at other sites.

Diagnosis rests on USG/CT followed by guided percutaneous aspiration to confirm the microbial etiology **(Fig. 15.2)**. Presence of elevated right hemidiaphragm with leukocytosis indicates possibility of liver abscess in a clinically suspected case.

Treatment: Drainage and appropriate antibiotics are mainstays of treatment in liver abscess.

Initial antibiotic regimen should be directed against gram-positive aerobes, gram-negative bacilli, and

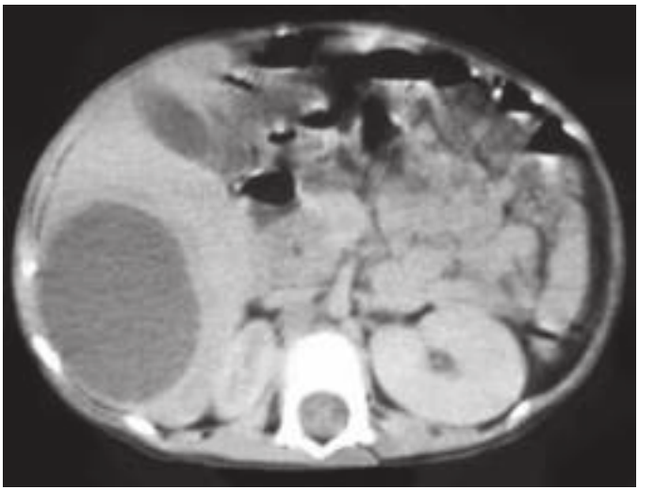

Fig. 15.2: **Liver abscess.**

anaerobic organisms with subsequent modification according to culture reports for a total duration of 4–6 weeks. Serial USG may be required to assess the response to therapy.

Percutaneous drainage is indicated where lesions are accessible under CT or ultrasound guidance. Catheters placed via these techniques are generally left in place until abscess collapse (*pig tail*). Open surgical drainage may be required if percutaneous drainage is not feasible or fails.

15.7 CHRONIC LIVER DISEASE

Chronic liver disease (CLD) denotes *persistent hepatic dysfunction for >6 months*, with or without clinical symptoms, often culminating into irreversible or end-stage hepatic disease.

Etiology: HBV is the commonest cause of CLD in Indian children, followed by cholestatic syndromes and autoimmune liver disease **(Table 15.10)**.

Pathologically, CLD may be classified as:

- *Chronic persistent hepatitis*, without jaundice and with mild/moderate elevation of liver enzymes. Hepatocellular inflammation in these cases is limited within portal triads.
- *Chronic lobular hepatitis*, more moderate disease with mixed intra-portal as well as centri-lobular inflammation. Mild jaundice is common.
- *Chronic active hepatitis*, with intra-portal and lobular inflammation as well as destruction of normal liver architecture. Definite signs of CLD and portal hypertension are present and most survivors progress to cirrhosis.
- *Cirrhosis* is the end-stage, characterized by—(a) shrunken liver, (b) extensive fibrosis, (c) destroyed liver architecture and (d) nodule formation.

TABLE 15.10: Causes of chronic liver disease

- **Infective**
  - *Hepatotropic virus infections:* HBV, HCV
  - Intrauterine (TORCH) infections
- **Metabolic liver disease**
  - *Common:* Wilson disease, Gaucher disease, GSD
  - *Rare:* Cystic fibrosis, Indian childhood cirrhosis
  - *Others:* Galactosemia, α1-antitrypsin deficiency
- **Drug/toxic liver injury**
  - Veno-occlusive disease
  - *Drugs:* Methotrexate, INH, etc.
- **Autoimmune liver disease**
- **Neonatal cholestasic syndromes (Table 12.41)**

GSD: Glycogen storage disorders

Depending on the nodular size, cirrhosis is also termed (a) *micronodular*, e.g. Indian childhood cirrhosis, biliary cirrhosis, etc.; (b) *macronodular*, e.g. Wilson disease, post necrotic/hepatitic cirrhosis, etc. or (c) *mixed*, e.g. metabolic liver diseases, etc.

Clinical spectrum of CLD ranges from—(a) asymptomatic biochemical abnormalities, to (b) signs of progressive liver disease, or (c) signs of acute decompensation over pre-existing liver disease. Liver may or may not be palpable, depending on primary pathology. Important clinical features of CLD are tabulated in **Table 15.11**.

TABLE 15.11: Clinical indicators of chronic liver disease

Signs of impaired hepatic metabolism
- Icterus (s/o impaired bilirubin metabolism)
- Edema (s/o impaired protein metabolism)
- S/o fat malabsorption
  - Growth failure, steatorrhea, phrynoderma
- S/o Fat-soluble vitamin deficiency
  - Xerophthalmia (Vitanin A)
  - Rickets (Vitamin D)
  - *Bleeding:* epistaxis, GIT bleeds (Vitamin K)
- S/o impaired steroid metabolism
  - Spider nevi, palmar erythema, gynecomastia

S/o Portal hypertension
- Splenomegaly
- Ascites (also due to hypoproteinemia)
- *Others:* Esophageal varices, caput medussae

S/o Cholestasis
- Clay-colored stools
- Pruritis

S/o Primary disease
- *Autoimmune:* Arthropathy, hemolytic anemia, rash
- *Wilson disease:* KF ring, CNS signs

S/o Impending liver failure
- Altered behavior and sleep pattern
- Fetor hepaticus
- Flapping tremors

S/o: Signs of.

Laboratory investigations aim to assess and monitor the extent of liver damage as well as to identify the etiology and include:

- *To assess liver functions*:
  - Liver function tests
  - Coagulation profile
  - Radionuclide liver scan
  - Ultrasonography
  - Esophagoscopy for varices
- *To identify etiology*:
  - Liver biopsy
  - Serology, e.g. viral markers, autoantibodies
  - Selective tests for specific metabolic defects

Management of CLD includes specific therapy for primary cause, as well as supportive therapy to prevent and treat complications. Most cases can be managed at home after initial evaluation, though intermittent hospitalizations are often necessary to treat complications. Important supportive measures include:

- ***Nutritional management:*** *Diet* in CLD should provide 120–150% of caloric requirements with ~50% as carbohydrates, 25–30% as fats and rest as good-quality proteins. Medium chain triglycerides are preferred as fats, which do not require bile for absorption. Protein restriction (~1 gm/kg/d) is necessary only in cases with impending liver failure, while salt-restriction is advised in presence of ascites.

  All cases should be supplemented with fat-soluble vitamins-vitamin A (5000–10000IU/day), vitamin D (2000–5000 IU/day), vitamin K (2–5 mg/week) and vitamin E (15–25 IU/kg/day).
- ***Management of ascites:*** Ascites in CLD is contributed by portal hypertension as well as hypoproteinemia and must be managed by:
  - *Dietary sodium restriction* to maximum of 5 gm/day. Fluid restriction is unnecessary, except in hyponatremia.
  - *Diuretic therapy*, preferably with potassium-sparing *spirolactone* (PO 1–3 mg/kg/d). Loop diuretics or thiazides are used in severe cases.
  - *Abdominal paracentesis* is required in large ascites with respiratory embarrassment. Amount of tapped fluid at one sitting should not exceed 10–15% of body weight, to prevent hypovolemia. Simultaneous administration of albumin or plasma expanders is advisable in large-volume paracentesis.
- ***Management of bleeding*****:** Intermittent bleedings is common in CLD due to esophageal varices or vitamin K deficiency and should be managed according to the cause and severity, with blood transfusions, vitamin K therapy and endoscopic therapy, whenever indicated. (Ch 15.9).
- ***Management of hepatic failure*****:** All cases should be periodically monitored for impending liver failure and managed accordingly (Ch 15.5).
- ***Specific management*** includes use of penicillamine in Wilson disease, Entecavir or Sofosbuvir/Velpatasvir in HBV or HCV respectively and steroids in autoimmune hepatitis, discussed later in this chapter.
- ***Liver transplant*** is last resort in cases with poor response to above measures and repeated hospitalizations. However, it is *contraindicated* in—(a) multisystemic metabolic disorders, (b) metastatic malignancies, and (c) during acute hepatic failure. Outcome of liver transplant depends on primary disease, though overall 5-year survival is >50–60%. *Complications*, e.g. graft-rejection, opportunistic infections and reappearance of disease are common.

Outcome of CLD depends on primary etiology and extent of liver damage. Most cases of chronic persistent or lobular hepatitis recover spontaneously. Chronic active hepatitis has poorer prognosis with eventual development of cirrhosis and occasionally, secondary carcinoma. Many patients may also develop hepatorenal syndrome.

Hepatopulmonary syndrome is a triad of: (a) chronic liver disease or portal hypertension, (b) wide alveolar-arteriolar gradient with/out hypoxemia, and (c) intrapulmonary vascular dilatations. It presents with progressive hypoxia, cyanosis and clubbing, with echocardiography suggestive of intrapulmonary shunting. Liver transplant is required in all cases.

Some important causes of CLD are discussed here in greater details:

Chronic hepatitis B infection (HBV), defined as *persistence of HBsAg positivity for > 6 months*, is the one of the commonest causes of CLD in Indian children, accounting for >40% cases. About 3–7% of Indian population is HbsAg positive (carrier), of which ~35–40% are likely to develop CLD.

Three different phases have been described in natural course of HBV infection:

- *Immune tolerance phase* with active viral replication (high HBV-DNA levels in millions) but minimum liver damage (normal ALT). While HBsAg and HBeAg are positive, anti-HBeAg antibodies are absent.
- *Immune clearance phase* after many years with clearance of infection (reduced HBV-DNA levels) but progressive liver injury with/without symptoms (elevated ALT). Serology continues to be same with positive HBsAg and HBeAg and negative Anti-HBeAg antibodies.
- *Inactive carrier phase* with resolution of liver injury (normal ALT) and infection (very low HBV-DNA levels) as well as reversal of HBe serology, i.e. HBeAg negativity with presence of anti-HBeAg antibodies. Most of these cases remain HBsAG positive despite being asymptomatic carriers, before turning HBsAg negative after 15–20 years.

Diagnosis of chronic HBV infection depends on: (a) clinical evaluation with Liver function tests, (b) serology including quantitative HBV-DNA, and (c) liver biopsy in cases with elevated ALT levels, for staging of disease. All these cases should also be tested for HCV and HIV due to common mode of infection.

Management: As per recent guidelines, these cases are divided into two groups-those with *chronic HBV infection* (normal ALT) and those with *chronic HBV hepatitis* (raised ALT), second group needing liver biopsy.

All cases with chronic HBV Hepatitis having persistent elevation of liver enzymes and/or evidence of active disease on liver biopsy need treatment under expert guidance with:

- Subcutaneous interferon (5–10 million units/m^2 thrice weekly) in children < 2 years or Pegylated interferon- 2a/b in older children of 2–18 years, for 6–10 months to inhibit viral protein synthesis.
- Oral antivirals, e.g. Entecavir (0.5–1 mg/day) or Lamivudine (3 mg/kg/day) in children aged -2 years and Tenofovir (300 mg OD) or Adefovir (10 mg OD) in adolescents >12 years, for 1–8 months.

Both groups of drugs may be used concurrently or sequentially in different regimens. Treatment should continue till normalization of liver function tests, undetectable HBV-DNA or HBeAg and resolution of histopathology. Success rate is ~ 40–60%.

Autoimmune hepatitis (AIH) is responsible for ~10% cases of CLD in children, characterized by:

- Chronic hepatocellular inflammation on biopsy,
- Presence of liver-specific autoantibodies, and
- Co-existing autoimmune disorders, e.g. arthropathy, rash, hemolytic anemia, thyroiditis, etc.
- Response to immunosuppressive therapy

Etiology: Although autoimmune in origin, exact triggers are unknown, probably related to genetic predisposition or preceding viral/drug exposure.

Pathologically, liver biopsy reveals distorted hepatic architecture of variable severity, including—(a) inflammatory infiltrates, (b) piecemeal and bridging hepatic necrosis, (c) bile duct epithelial injury, and (d) interface hepatitis.

Clinically, AIH predominantly presents in young females with three different presentations:

a. *Acute hepatitis* like presentation in 3–0%, rapidly progressing to AHF;
b. Insidious-onset liver disease with waxing and waning course in another 3–0%
c. *Chronic liver disease* with complications, e.g. ascites and portal hypertension in 1–0%

Extrahepatic manifestations, e.g. arthritis, vasculitis, nephritis, Coombs-positive anemia, and rash are not uncommon.

Diagnosis rests on liver biopsy and serological studies. According to the type of autoantibodies, AIH is divided into type I in 6–0% (ANA/SMA antibody positive), type II in 2–0% (LKM1 antibody positive) and type III (SLA antibody positive, in young females). Hypergammaglobulinemia is common with IgG levels often exceeding 16 g/L. Other causes, e.g. viral hepatitis or Wilson disease must be excluded.

Treatment includes long-term immunosuppression with steroids and azathioprine. While >80% cases achieve remission with treatment, relapses are common after discontinuation of therapy.

Prednisolone is started as PO 1–2 mg/kg/day until serum ALT values normalize, followed by gradual tapering to a maintenance dose of 0.1–0.3 mg/kg/d till normal liver histology. In cases with poor response or side-effects, Azathioprine (PO 1.5–2.0 mg/kg/d) may be added. Mycophenolate, Tacrolimus and Rituximab are other options.

Wilson disease is a common disorder of copper metabolism (1:10000–00000 births), clinically characterised by a triad of—(a) *chronic liver disease*, (b) *neurological signs,* and (c) *kayser-Fleischer* (KF) *ring* over cornea.

Etiopathogenesis: It is an autosomal recessive disorder involving chromosome 13, with *basic defect in mobilization of copper from hepatocytic lysosomes* due to mutations in gene ATP7B.

In fetal life, high *metallothionein* (copper-binding protein in tissues) with low *ceruloplasmin* (copper-binding protein in plasma) activity facilitates deposition of copper in tissues. Normally, this pattern reverses to adult pattern of low-metallothionein/high-ceruloplasmin levels by 2 years of age. Failure of this switch-over in Wilson disease leads to accumulation of copper in hepatocytes and consequent destruction. Escaped copper from hepatic cells also leads to systemic copper deposition and toxicity in other tissues, e.g. brain, cornea, kidneys and joints.

Clinically, age and mode of presentation in Wilson disease usually follows a familial pattern. Most cases present between 5–10 years of age with:

- *Hepatic involvement*, as the earliest feature, presenting with hepatomegaly, jaundice, sub-acute hepatic failure and portal hypertension.
- *Neurological manifestations* usually after the first decade with intention tremors, dysarthria, dystonia, rigidity, chorea and behavioral changes. Preceding liver involvement is common but not mandatory.
- *Ocular manifestation*, i.e. development of a rusty-brown *Kayser-Fleischer ring* over cornea is usually present at the time of liver disease **(Fig. 15.3)**.
- *Systemic complications* due to involvement of other tissues are seen in long survivors, as Fanconi syndrome, hemolytic anemia, chronic arthropathy and endocrinopathies.

Diagnosis: *Low serum ceruloplasmin level (<20 mg/dl) is the best screening test for Wilson disease,* supported by elevated

Fig. 15.3: **Kayser-Fleischer ring in Wilson disease.**

urinary copper levels (>100 µg/day). Serum copper may be low, normal or elevated.

Diagnosis is conventionally confirmed by:

- Penicillamine challenge test, i.e. >5–10 fold rise in urinary copper excretion (>1000 µg/day) after two doses of d-penicillamine (PO 500 mg/dose at 12-hr interval),
- Increased copper content in dry liver tissue (>250 µg/gram of liver tissue).

However, combination of—(a) low serum ceruloplasmin, (b) presence of KF ring, and (c) elevated 24-hr urine copper may be used to confirm the diagnosis of Wilson's disease.

Penicillamine challenge test is not routinely recommended n due to high false-positivity and liver copper estimation is not easily available with quality issues. Uneven copper distribution in liver limits its usefulness. High liver copper may also be present in cholestatic liver disorders.

Family screening with serum ceruloplasmin and urinary copper levels is necessary.

Management revolves around the cop*per chelation therapy* by PO Penicillamine (20 mg/kg/day q12hr) to increase urinary excretion. Uncommon but significant toxicities of penicillamine include SLE, aplastic anemia and nephrosis.

In cases with penicillamine intolerance or toxicity, alternative copper chelator *Trientine* (Triethylenetetramine-2-dihydrochloride) may be used.

Zinc may be added to decrease gut copper absorption (PO 25 mg/kg/day q8hr).

Outcome: Early chelation therapy is most important determinant for outcome, which leads to complete resolution of liver histology and disappearance of KF ring. Untreated cases die due to AHF or renal/neurological complications. Chelation therapy is indicated even in asymptomatic siblings.

Indian childhood cirrhosis (ICC), was a unique disease limited to Indian subcontinent, extremely rare at present.

Epidemiology: ICC was almost exclusively seen in children aged 6 months-3 years, more common in males, top-fed children and certain communities—North-Indian banias and south-Indian Brahmins.

Etiopathogenesis yet remains uncertain, proposed to be infective, immunological, toxic, metabolic or nutritional injury to hepatocytes. Most acceptable one is the role of increased copper deposition in liver either due to altered metabolism or increased dietary intake due to cooking/water storage in copper/brass vessels.

Clinically ICC commonly presented as gradually progressive disease with 3 stages:

a. ***Pre-icteric stage*** (3–6 months), with abdominal distension, failure to thrive, anorexia, and altered behavior. Moderate hepatomegaly with *typical firm consistency, sharp-leafy margins and finely nodular surface* was pathognomonic..
b. ***Icteric stage*** with gradual increase in liver size, jaundice and portal hypertension with splenomegaly and ascites.
c. ***Terminal stage*** of liver failure with bleeding diathesis and encephalopathy.

Diagnosis rested onliver biopsy showing: (a) complete destruction of liver architecture with nodule formation, (b) diffuse creeping fibrosis without regeneration, (c) increased copper content on orcein staining, and (d) presence of *Mallory's hyaline bodies*—clumps of eosinophilic hyaline material, in 15–20%.

Management: ICC was almost always fatal, though very few cases have recovered spontaneously. Apart from supportive measures attempts were made to treat ICC with immunomodulatory drugs, e.g. steroids, or copper chelators, e.g. d-penicillamine, with equivocal results.

Non-alcoholic fatty liver disease (NAFLD) or steatohepatitis (NASH) is a common but benign cause of chronic liver disease, usually associated with obesity and insulin resistance.

NAFLD is a pathological diagnosis with macrovesicular steatosis, without inflammation or with inflammation, later termed as NASH.

Clinically, most children are obese and asymptomatic or present with vague abdominal pain and moderate hepatomegaly. Acanthosis nigricans (velvety brown-black pigmentation over nape of neck, axilla and skin folds) is common in 3–0% cases, often associated with hyperinsulinemia due to insulin resistance.

Diagnosis: Although radioimaging procedures can detect fatty liver, biopsy may be necessary in some

cases to exclude serious pathologies. Non-invasive measurements of fibrosis by transient elastography or acoustic radiation forced impulse may be useful to avoid biopsy. Liver enzymes may be elevated, along with hypertriglyceridemia and hyperglycemia despite hyperinsulinemia.

Management aims to reverse the liver disease by life styles changes to control obesity, e.g. dietary modifications and exercise. Most cases respond well to weight reduction and vitamin D or E supplementation. Progression to cirrhosis is very rare.

Congenital hepatic fibrosis, an autosomal recessive disorder, is an important cause of portal hypertension. These cases usually present in late childhood with hepatosplenomegaly and esophageal varices with intermittent hematemesis. Liver biopsy is diagnostic with diffuse periportal and perilobular fibrosis in broad bands, containing distorted duct-like structures or microcyst formation. Renal disease, e.g. polycystic kidney is present in ~ 3/4th cases.

Management includes control of esophageal bleeding/varices and treatment of renal disease. Some cases may need shunting procedure.

Caroli disease, i.e. congenital saccular dilatations of intrahepatic cuboidal epithelium, may be an isolated defect or associated with congenital hepatic fibrosis and polycystic kidneys (***Caroli syndrome***). Both variants are autosomal recessive. Most cases present with recurrent acute cholangitis and gallstones, before development of portal hypertension.

15.8 PORTAL HYPERTENSION

Portal hypertension (PHT) is defined as '*elevation of portal venous pressure >12 mm Hg*, due to hepatic or extrahepatic obstruction in portal blood flow'.

Portal vein is formed by joining of splenic and superior mesenteric veins and carries most of the gastrointestinal blood flow to liver for further metabolism of absorbed nutrients.

Etiologically, PHT may be broadly classified as—*(a) prehepatic* or extra-hepatic, *(b) hepatic*, and *(c) post-hepatic* or post-sinusoidal *obstruction* **(Table 15.12)**. Extrahepatic PHT accounts for ~75% cases in Indian children. Umbilical sepsis or cannulation in neonatal period is the commonest cause of extrahepatic PHT.

Pathogenesis: Irrespective of etiology, primary hemodynamic abnormality in PHT is the obstruction in portal blood flow, leading to:

a. Development of collateral flow (porto-caval shunts), e.g. *esophageal varices*, *rectal hemorrhoids* or periumblical *caput medussae*.
b. Chronic hepatic ischemia, with compromised liver functions.

TABLE 15.12: Causes of portal hypertension

- **Pre-hepatic or extrahepatic**
  - Umblical sepsis/cannulation in newborns
  - Dehydration/septicemia in early infancy
  - Acute peritonitis in older children
  - *Hypercoagulable states:* Protein C or S deficiency
  - Portal vein malformations, e.g. AV fistula
- **Intra-hepatic (Chronic liver disease)**
  - Congenital hepatic fibrosis
  - Chronic viral/autoimmune hepatitis
  - Cirrhosis
  - Metabolic disorders, e.g. Wilson disease
  - Hepatic tumors
  - Cholestasis, e.g. total parenteral nutrition
- **Post-hepatic or post-sinusoidal**
  - Budd-Chiari syndrome
  - Veno-occlusive disease of liver
  - Constrictive pericarditis

c. Cavernous transformation of portal vein (acquired portal cavernoma).

Clinical features of PHT depend on the site of obstruction, severity of portal pressure and extent of collateral flow. Important features include:

- *Recurrent GIT bleeding* as hematemesis or melena is the common, originating from esophageal varices. Hemorrhoids are uncommon in children. Hematemesis may be preceded by mild respiratory infections and cough (increase in intra-abdominal pressure) or drug intake, e.g. salicylates.
- *Dilated periumbilical veins* (*caput medussae*) with blood flow *away from umbilicus*, i.e. reversal of normal direction. Engorged veins with upward flow in abdominal flanks indicate inferior vena cava obstruction in post-hepatic PHT.
- *Splenomegaly* with/without hypersplenism is invariably present, though the size may reduce temporarily after GIT hemorrhage.
- *Signs of chronic liver disease*, e.g. ascites, icterus, hypoproteinemic edema and spider nevi, etc. are common in hepatic/post hepatic PHT, but not in extrahepatic PHT.
- *Hepatic encephalopathy* may develop after severe GIT bleeds due to further compromise of hepatic blood flow, though uncommon in extrahepatic PHT.
- *Secondary complications*, e.g. anemia, shock are often present, immediately after severe bleeds.

Important clinical differences between various types of PHT are summarized in **Table 15.13**.

Diagnostic investigations in PHT include:

- *Ultrasonography* to confirm the site of obstruction, estimate portal vein size, and visualize esophageal varices. Doppler flow studies may demonstrate reversed blood flow in portal circulation.

TABLE 15.13: D/D portal hypertension

	Extra-hepatic	*Hepatic*	*Post-hepatic*
Past history of…	U. sepsis*	liver disease	–
Hepatomegaly	–	+/-	++ tender***
S/o liver failure	-/+	++	+/-
Distended veins	Central	Central	Lateral**
Pedal edema	-/+	++	+/-
Diagnostic investigation	USG	LFT	Venogram

*or umblical cannulation, **S/o Inferior vena caval obstruction.
***in acute cases

- *Liver function tests* including coagulation profile in all cases, even in absence of clinical signs, to assess baseline liver functions.
- *Endoscopic visualization* of esophageal varices in all cases at the time of diagnosis, which may ligated at the same time.
- *Contrast studies*: IVC venogram is indicated in unexplained post hepatic PHT, e.g. Budd-Chiari syndrome, to localize the site of obstruction. Selective angiography is rarely necessary, except before surgery for precise mapping of portal flow.

Management of PHT depends on the clinical state at the time of presentation and includes—(a) emergency hemodynamic support, (b) control of active bleeding, and (c) prevention of further bleeding.

- **Emergency hemodynamic support** includes: (a) fluid and electrolyte correction, (b) blood transfusion in severe anemia, (c) vitamin K supplements, (d) continuous nasogastric drainage to detect and quantify further bleeding, and (e) H_2 receptor antagonists, e.g. ranitidine to reduce gastric bleeding.
- **Control of active bleeding** with *endoscopic ligation of bleeding varices* by elastic *bands* or *sclerotherapy* is the treatment of choice in active hematemesis, though subsequent endoscopies may be required to ligate/sclerose all varices. Complications include infection, traumatic ulcerations and stricture formation in esophagus.

  Following emergency medical measures may be useful, if endoscopic facility is not available:
  - *Splanchnic vasoconstrictors* to reduce portal flow and pressure, with *Octreotide*, (IV 1–10 µg/kg Q12hr) or Vasopressin (IV 0.33 U/kg bolus over 20 min followed by 0.2 U/1.73 m^2/min), till bleeding is controlled.
  - *Sengstaken-Blackmore tube*, passed nasogastrically to apply mechanical pressure over bleeding varices. However, re-bleeding after removal and pulmonary aspiration is common.
- **Prevention of further bleeding:** Ligation of esophageal varices and periodic follow-up is usually enough for most cases. However, selected cases may require portacaval shunts and treatment of primary cause, including liver transplants.

Portacaval shunts, e.g. proximal linorenal shunt, are indicated in severe PHT with recurrent bleeding to reduce portal venous pressure. However, shunt-thrombosis and further hepatic ischemia with acute liver failure are common. Shunt procedures also make later liver transplant surgery difficult. *Trans-jugular intra-hepatic porto-systemic shunt (TIPS)*—a stent placed by interventional radiologist between right hepatic vein and portal vein is preferred in sick cases or those who may need liver transplant in future.

Long-term therapy with-blockers, e.g. propranolol (PO 1–2 mg/kg/d) may also reduce the risk of variceal bleeding and improve survival.

Prognosis is poor in cases with hepatic disease. In extrahepatic PHT, frequency of bleeding often reduces with age due to development of collaterals and most patients can be successfully managed with periodic variceal ligation/sclerotherapy.

Important late complications of PHT include hepatorenal syndrome (Ch 15.8) or Porto-pulmonary syndrome, i.e. pulmonary artrerial hypertension > 25 mmHg with severe PHT, usually following cirrhosis.

Budd-Chiari syndrome (BCS) due to occlusion of hepatic veins or suprahepatic inferior vena cava due to intraluminal thrombus or web (primary BCS) or extraluminal pressure, e.g. tumors, is an important cause of post-hepatic PHT.

While most patients have insidious course with hepatomegaly, ascites and PHT, acute BCS presents with abdominal pain, tender hepatomegaly and rapidly progressive liver failure with ascites. Back and flank veins are dilated and tortuous, with flow from below-upward.

Diagnosis may be confirmed by Doppler studies and venography.

Treatment requires restoration of venous patency by stenting or transjugular intrahepatic porto-systemic shunt. Surgery is rarely required, though terminal cases may need liver transplant.

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CHAPTER

16

Respiratory Disorders

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Acute respiratory infections are leading causes of post-neonatal mortality in Indian children.

16.1 BASIC CONSIDERATIONS

Respiratory tract may be divided into two broad segments: (a) *Upper respiratory tract* extending from nose to oropharynx and including related structures, e.g. paranasal sinuses and ears, and (b) *Lower respiratory tract* including *Airways*, e.g. larynx, trachea and bronchi as well as *lungs*.

Anatomically, lungs are paired structures, located on both sides of mediastinum in thoracic cavity and covered with two layers of pleura. Each lungs is divided into lobes by pleural invaginations and septa (3 on Rt side/2 on Lt side) and further into bronchopulmonary segments (10 on Rt side/8 or 9 on Lt side), ach with independent bronchial and blood supply **(Fig. 16.1)**. These lobes and broncho-pulmonary segments restrict direct progression of disease.

Histologically, lung is a spongy tissue with three important components: (a) *airway structures*, i.e. distal bronchial tree, (b) *alveoli*-the air-blood interface area, each supplied by own respiratory bronchiole, and (c) *interstitial spaces* with network of capillaries.

Airways are lined by ciliated epithelial membrane that gradually changes from pseudo-stratified columnar epithelium in upper airways to cuboidal epithelium in terminal respiratory bronchioles. Smooth muscle content of airways also declines distally. Presence of cilia, mucus-secreting goblet cells and immunological cells in lamina propria are important defence barriers in airways.

Lung surfactant is a heterogeneous mixture of phospholipids and proteins, secreted into alveoli from 24th week onwards, by specialized alveolar cells – type II pneumocytes. Lining the alveoli, surfactant prevents end-expiratory alveolar collapse and facilitates their re-expansion by reducing the surface tension (Ch 12.13).

Embryologically, respiratory system develops from two different sources:

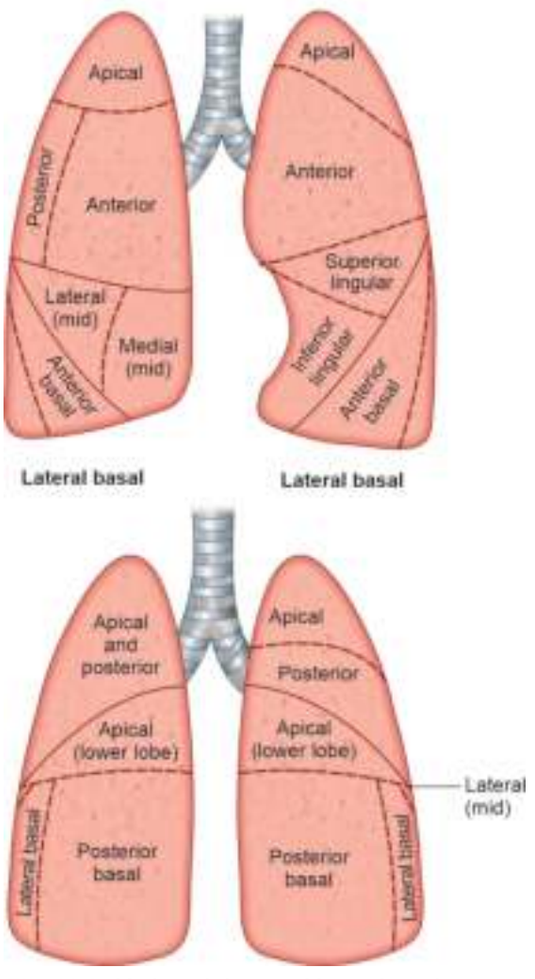


Fig. 16.1: Various lobes and bronchopulmonary segments in lungs.

a. ***Airways*** develop as a *ventral out-pouch or diverticula from the endodermal epithelium of the primitive foregut,* which divides to form two main-stem bronchial buds and burrow into surrounding mesenchyme that separates foregut from the coelomic cavity. These buds branch further to develop into complex bronchial tree and alveoli, passing through various

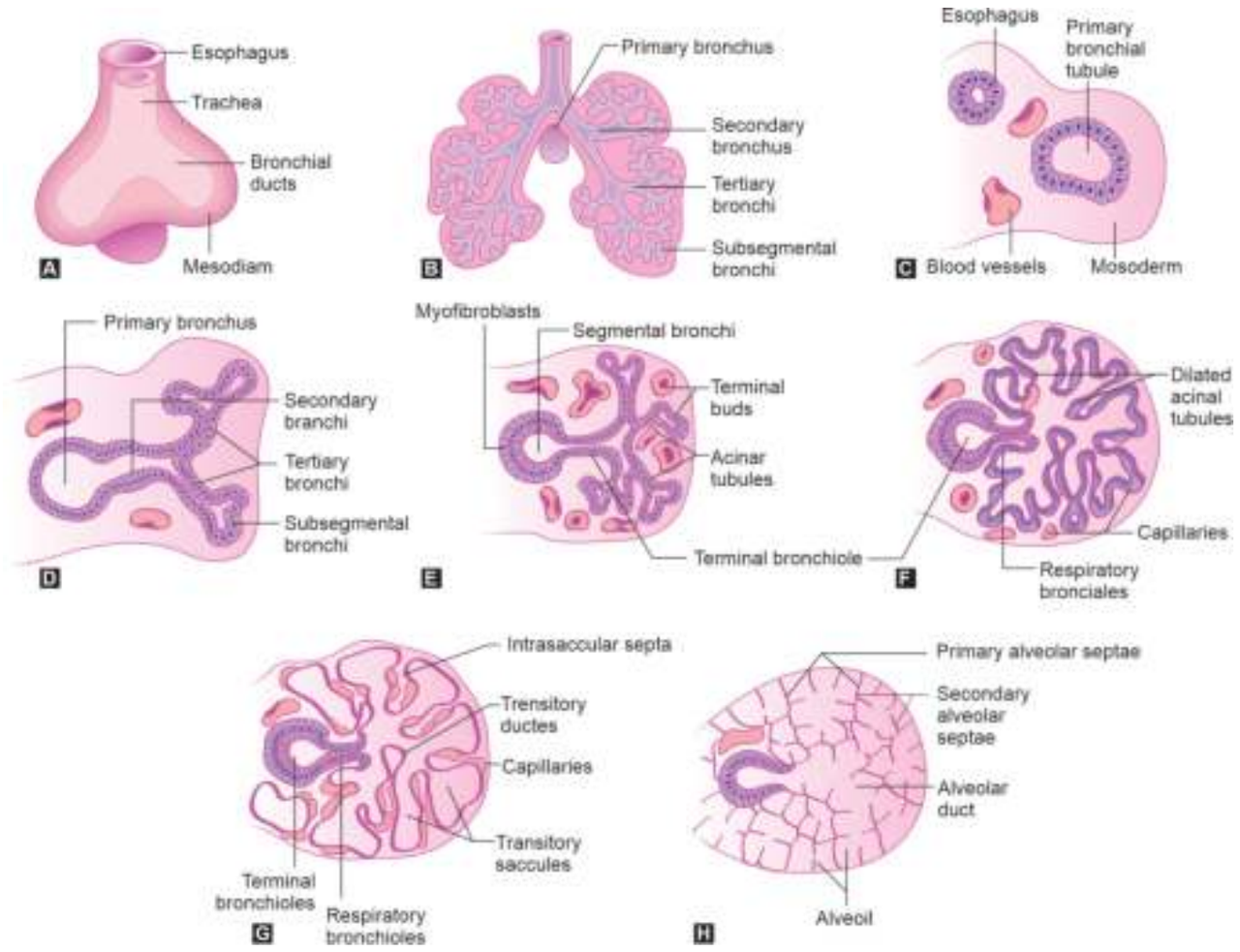


Fig. 16.2: Development of respiratory system: (A) Early embryonic period; (B) Late embryonic period; (C) Early embryonic period; (D) Late embryonic period; (E) Pseudoglandular stage; (F) Canalicular stage; (G) Saccular stage; (H) Alveolar stage.

stages of development, i.e. *(a) embryonic period, (b) pseudoglandular period, (c) canalicular period and (d) alveolar period* **(Fig. 16.2)**. Lining cells of these buds differentiate into ciliated, secretary, globular or neuroendocrinal cells, each with specialized function.

b. ***Pulmonary vasculature and supporting structures***, e.g. pleura, alveolar septa, interstitium, smooth muscles and cartilaginous part of airways, develop from *mesenchymal* tissue. Soon after their appearance, bronchial buds are surrounded by a vascular plexus from systemic circulation that gradually connects with pulmonary artery/veins to complete pulmonary circulation by 7th week of life. However, some connection from systemic circulation is retained via bronchial vessels throughout the life, which may be life-saving as collaterals in cases of severe pulmonary vascular obstruction, e.g. heart diseases with pulmonary stenosis.

About 50 million alveoli are present at birth. In first 2 years of postnatal life, alveoli continue to grow in numbers and volume, though vascular growth is disproportionately more than alveolar growth. After 2 years, most of alveolar growth is in terms of volume rather than in numbers.

Fetal lung development depends on many factors, the most important being:

- *Specific gene families*, i.e. Hox a-1, 2, 3, 5 and Hox b-3, 4, 6, 7, 8 which regulate branching of airways and differentiation/maturation of lung cells,
- *Fetal lung secretion*, essential for development of acini, and
- *Hormones*, e.g. steroids and thyroid hormones, which regulate surfactant production.

Respiratory Defense Mechanisms

Lungs are constantly exposed to external environment containing pathogens, allergens and other pollutants. Important defence mechanisms to protect the lungs and respiratory tract from this onslaught are shown in **Table 16.1**.

These defense mechanisms may be impaired by—(a) *Environmental insults*, e.g. smoking and air pollution,

TABLE 16.1: Respiratory defense mechanisms

- **Mechanical**
  - Nasal filtering, warming, humidification of air
  - Cough reflex
  - Mucociliary clearance in airways*
  - Collateral alveolar ventilation**
- **Immunological**
  - Phagocytosis by alveolar/interstitial macrophages
  - Secretary IgA to inactivate pathogens and toxins
  - IgM/IgG mediated immune response
  - IgE mediated allergic/inflammatory response
  - *Others:* Opsonins, lysozymes, interferon, etc.

*upward movement of mucus at the rate of 10 mm/minutes
**via pores of Kohn and canals of Lamberts

exposure to cold, (b) *Pathological insults*, e.g. starvation, hypoxia, acidosis and viral infections, (c) *Hypersensitivity reactions*, e.g. asthma or allergic rhinitis, (d) *Drugs*, e.g. steroids, anesthetics and narcotics, and (e) *Vascular disturbances*, e.g. pulmonary edema/embolism.

Physiology of Respiration

In utero, gaseous exchange depends exclusively on placenta. Act of breathing is absent and fetal lungs are-(a) filled with a specific fluid, actively secreted by alveoli and mixed with amniotic fluid, (b) receive <2% of total cardiac output.

An electrolyte-rich fluid is constantly produced and filled in fetal alveoli, essential for their development. However, presence of this fluid is incompatible with postnatal alveolar breathing and its secretion declines in late gestation.

At birth, gaseous exchange system switches-over from placental to pulmonary dependence, with following major adaptive mechanisms:

- Initiation of central respiratory drive, due to mechanical stimulation of baby and sudden hypoxia after severance of placental circulation,
- Switch-over from parallel to sequential pulmonary and systemic circulation,
- Absorption of fetal lung fluids to create an air-blood interface in alveoli, separated from highly porous and permissible alveolar epithelium,
- Increased production and spread of surfactant over inner alveolar lining, to prevent end-expiratory collapse and facilitate re-expansion.

Postnatal respiration: Primary aim of respiration is to provide adequate gaseous exchange, which requires-(a) adequate ventilation of alveoli, (b) adequate perfusion of interstitial capillary network, and (c) adequate diffusion of gases across the alveolar membranes. Some important aspects of these mechanisms are as follows:

A. Ventilation (breathing) physiology is complex and still evolving, though four components play a major role in regulation of normal breathing:

a. *Afferent feedback* from—(a) stretch/temperature-sensitive receptors, located in larynx and upper airways (via superior laryngeal nerve); (b) chemoreceptors located in carotid or aortic bodies, sensitive to arterial O_2 and CO_2 tensions (via carotid/aortic sinus nerves); (c) skin, mucosal or hypothalamic receptors, sensitive to thermal or metabolic changes.

b. *Central controller* located in medulla, tentatively identified and named as *nucleus tractus solitarius, nucleus ambiguous/retroambiguus and pre-botzinger nucleus*. However, these centers act as the controller of breathing and not the generator of normal rhythm, which is yet unidentified. *Note* that respiratory control mechanism operates on negative feedback and not the positive feedback, i.e. central controllers merely attempt to rectify any deviation from normal breathing.

c. *Efferents* are conveyed via phrenic nerve to diaphragm and other muscles of respiration.

d. *Effectors (respiratory muscles):* Diaphragm and intercostals are most important muscles in breathing, though the relative contribution varies with age. Breathing during early infancy is mainly intercostals-dependent (thoraco-abdominal) that gradually switches-over to mature diaphragm-dependent breathing (abdomino-thoracic) by the end of infancy. Other muscles, e.g. nasal, orophraryngeal and neck muscles also support the breathing efforts, though their contribution is minor (accessory muscles), except during high demand, i.e. hypoxia and respiratory distress.

B. Pulmonary perfusion: After initial hemodynamic changes at birth (Ch 17.1.3), pulmonary circulation offers much lower resistance to blood flow than systemic circulation. However, pulmonary resistance depends on two important factors—(a) intrathoracic pressure, (b) alveolar/blood gases.

Intrathoracic pressure affects the pulmonary resistance by mechanical means. During inspiration, alveolar vessels compress while extra-alveolar vessels dilate, leading to net changes in pulmonary resistance. As the effect of lung inflation predominates over extra-alveolar vessels at low lung volume and alveolar vessels at high lung volume, pulmonary resistance decreases at lower lung volumes and increases at higher lung volumes - a phenomena with considerable significance during mechanical ventilation.

Pulmonary arterioles are highly sensitive to alveolar hypoxia and hypercarbia-responding with vasoconstriction that allows re-shunting of non-oxygenated blood away from poorly ventilated areas. However, severe or persistent hypoxia/hypercarbia may lead to severe pulmonary hypertension and cardiac failure. Prolonged changes in pulmonary resistance due to

chronic hypoxemia or overdistended alveoli can produce smooth muscle hypertrophy with progressive vascular obstruction, leading to development of pulmonary arterial hypertension and *cor pulmonale* in chronic lung diseases.

Pulmonary circulation is also the site of active exchange of water and solutes between vascular space and lung interstitium via endothelial cells or inter-endothelial cell junctions. This exchange is regulated by relative hydrostatic and osmotic gradients as well as vascular permeability. Abnormalities of this exchange are responsible for pulmonary edema, seen in many conditions, e.g. left heart failure, pulmonary venous hypertension and acute respiratory distress syndrome (ARDS).

C. Pulmonary diffusion: Gaseous diffusion across the alveolar epithelium depends on many factors—(a) fractional oxygen concentration in inspired air or FiO_2, (b) partial pressure of O_2/CO_2 in venous blood, (c) Oxygen carrying capacity of hemoglobin, and most importantly, (d) alveolar ventilation and perfusion.

Relative ventilation and perfusion in different parts of lung is a critical determinant of net pulmonary diffusion and tissue oxygenation. All parts of lungs are not equally ventilated or perfused. Normally, the *upper parts of lungs are better ventilated and lower parts are better perfused.* In disease, ventilation and perfusion in different parts of lung may be affected proportionately or disproportionately, leading to altered ventilation-perfusion ratio and consequent hypoxia/hypercarbia.

Since air-blood barrier in the lungs has lower diffusion conductance for O_2 than for CO_2, arterial pO_2 is closer to alveolar pO_2 than alveolar: arteriolar pCO_2 relationship. Normal alveolar: arteriolar pO_2 difference is 5–6 mm Hg, due to normal channels of pulmonary-bronchial shunting. Higher alveolar-arterial oxygen difference indicates adverse changes in ventilation-perfusion ratio, seen in many respiratory disorders.

16.2 CLINICAL EVALUATION OF RESPIRATORY DISEASE

Cough and respiratory distress are primary indicators of respiratory disease, apart from others, e.g. wheeze, stridor, etc. Important components of clinical evaluation in these cases are as follows:

A. History in respiratory disease shall include details of presenting complaints, specially related to the *age of onset, duration and progression.*

Most cases present with acute, recurrent or persistent-(a) cough, (b) respiratory distress, (c) wheezing and/or (d) stridor. Generally, congenital defects present at birth or in early infancy, viral infections at all ages, bacterial infections mainly in younger or immunocompromised children, and tuberculosis usually after infancy.

Ill-sustained breastfeeding and hoarse cry may be the earliest indicators of respiratory distress in young infants and newborns. Unlike adults, hemoptysis and chest pain are rare in children.

Other important and relevant histories in respiratory disease include:

- *Associated complaints*, e.g. fever, weight loss, ear/ nose discharge, headache and dysphagia.
- *Preceding viral illness*, e.g. measles, suspected aspiration or foreign body inhalation.
- *Past history* of similar or other respiratory illness (recurrence or complication)
- *Family history* of similar illness, atopic disorders *or* contact with tuberculosis, including sputum positivity and treatment status in the contact.
- *Environmental history* of overcrowding, air pollution, passive smoking or similar illnesses in community.

B. General examination must specifically aims to look for: (a) fever, (b) severity of respiratory distress including cyanosis, (c) superficial foci of infection, e.g. ENT disease, pyoderma, etc. (d) lymphadenopathy or other markers for tuberculosis, (e) signs of chronic lung disease, e.g. growth failure, clubbing, etc. and (f) cardiac or neurological problems, which may be the cause or effect of respiratory disease.

Respiratory distress (RD) is indicated by abnormalities of rate (*tachypnea*), depth (*dyspnea*) and/or regularity (*irregular or periodic breathing*) and presence of abnormal audible sounds.

Respiratory rate (RR) varies with age and other physiological stress, though RR >60/min below 2 months of age, >50/min from 2–12 months and >40/min in older children is considered as abnormal.

Tachypnea without significant dyspnea is mainly seen in non-respiratory conditions, e.g. fever, exercise, anemia, hysteria and restrictive lung disease, e.g. pleural effusion. *Bradypnea* with decreased RR indicates heavy sedation or narcotic poisoning.

Depth of breathing is indicated by amount of respiratory excursions. Intercostal indrawing, nasal flaring and/or use of accessory neck muscles indicate presence and severity of dyspnea. *Dyspnea disproportionately more than tachypnea*, usually indicates airway obstructions, e.g. asthma or croup.

Presence of *stridor* indicates upper airway obstruction, e.g. croup, while *wheeze* indicates obstructed lower airways, e.g. asthma or bronchiolitis. *Expiratory grunt* indicates severe parenchymal pathology, e.g. pneumonia.

Irregular breathing is normal in newborns (periodic breathing). Important pathological irregularities include *Chenye-Stokes breathing* (alternating apnea and hyperpnoea) in raised intracranial pressure, *Kussmaul breathing* (deep and rapid air hunger) in acidosis, and *Biot's breathing* (irregularly irregular) in meningitis.

TABLE 16.2: Diagnostic features of common lung lesions

	Consolidation	***Collapse***	***Effusion***	***Pneumothroax***
Trachea	Central	Same side	Opposite side	Opposite side
Trail sign	–ve	+ve	+ve	+ve
Chest wall	Normal	Flattening	Bulging	Bulging
Resp. movements	↓	↓	↓	↓
Percussion note	Dull	Dull	Stony dull[3]	Resonant, *coin test* +ve
VF/VR	↑	↓/↑	↓[3]	↓
Breath sounds	Bronchial[1]	Absent[2]	Absent[3]	Absent
Chest X-ray	Opacity with NO MS	Opacity with MS same side	Opacity with MS opposite side	Hyperlucency with MS opposite side

MS: Mediastinal shift
[1]Egophony and Whispering pectoriloquy in large, dense consolidation.
[2]Bronchial breathing with ↑ VR may be present in collapse with patent bronchus.
[3]Shifting dullness and suction splash indicates hydro/pyopneumothorax. Bronchial breathing and ↑VR/VF is common at air-fluid interface.

C. Respiratory system examination helps in localizing the site of lesion and probable pathology **(Table 16.2)**, based on-inspection, palpation, percussion and auscultation of chest.

I. Inspection mainly includes: (a) shape of the chest, (b) type of breathing, (c) symmetry of chest movements, and (d) position of mediastinum on *trail sign*. Superficial abnormalities of chest, e.g. scar, injury marks and pulsations should also be looked for.

- ***Shape*** of the normal chest is bilaterally symmetric, with transverse diameter exceeding AP diameter.
  - *Asymmetric flattening* with drooping of shoulders indicates collapse or bronchiectasis, while *asymmetric bulge* indicates pleural effusion or pneumothorax.
  - *Bilateral bulging* (Barrel chest) is common in asthma or recurrent chest infections.
  - *Abnormal chest shapes* are also seen in non-respiratory conditions, e.g. rickets (rosary, pigeon-chest, Harrison sulcus) cardiomegaly (sternal/precordial bulge) and spinal deformities.
- ***Type of breathing*** is normally thoracoabdominal in infancy and abdominothoracic in older children. Abdomen is pushed-out during inspiration due to downward movement of diaphragm to create negative intrathoracic pressure, and pulled-in during expiration to increase intrathoracic pressure. Important abnormalities include:
  - *Paradoxical breathing* (reversal of normal abdominal movements) in diaphragmatic paralysis
  - *Paucity of abdominal movements* in diaphragmatic paralysis, gross ascites/peritonitis and subdiaphragmatic abscess.
  - *Paucity of thoracic movements* in intercostals paralysis, pleurisy and inflammatory conditions of chest wall.
- ***Asymmetric chest movements*** indicate unilateral disease, with visually restricted movements always on affected site.
- ***Trail sign,*** i.e. unilateral prominence of sterno-cleidomastoid, denotes shift of trachea on the same side.

II. Palpation of chest includes: (a) assessment of mediastinal position, (b) chest movements, and (c) tactile vocal fremitus (TVF), apart from confirming inspection findings.

- ***Position of mediastinum*** is assessed by: (i) suprasternal palpation of trachea, and (ii) location of apex beat. Normally, trachea is central or slightly on right side, while apex beat is in 4–5th intercostal space, ~1 cm medial to left mid-clavicular line. Tracheal and apical shift is usually concordant, though normally located trachea with shifted apex beat may be seen in smaller lower lung lesions (and vice versa for upper lesions) and cardiac lesions. Mediastinum is:
  - *Central* in consolidation and other lesions
  - *Pulled* on same side in collapse or fibrosis
  - *Pushed* on opposite side in effusion/pneumothorax
- ***Chest movements*** may be confirmed by placing flat palms of two hands on opposite sides at identical location. Chest movements are restricted on affected side. *Diaphragmatic or intercostals paralysis* is confirmed *by strapping method*, i.e. increase in respiratory distress after strapping of abdomen by examiner's hand in intercostals paralysis and after strapping of thorax in diaphragmatic paralysis.
- ***Tactile vocal fremitus (TVF)-****the tactile perception of chest wall vibrations in response to phonation*, is not a reliable sign in children due to thin chest wall and should be correlated with vocal resonance (VR) on auscultation, discussed later. TVF is:
  - *Increased* over consolidation, as solid tissue is a better conductor of vibrations than air or fluid.

– *Decreased* over pleural effusion (dampening effect), pneumothorax or collapse (absence of air entry).

III. Percussion of chest includes percussion—(a) over different areas of lung, including isthmus, and (b) for cardiac contour, and (c) location of liver dullness. As percussion note is not uniform all over the chest (depends on density of underlying tissue), it should always be compared from opposite site. Percussion is unreliable in small or deep-seated lesions. Important percussion abnormalities are:

- *Dull or impaired* note in consolidation, collapse, fibrosis, thicken pleura and pleural effusion (stony dull).
- *Hyperresonant or tympanic* note in pneumothorax, emphysema and superficial cavity or cysts.
- *Shifting dullness*, i.e. change in percussion note after change of posture in hydropneumothorax.
- *Obliterated cardiac dullness* in left pneumothorax.
- *Liver dullness* is normally in 4–5th ICS. It may be abnormally high in liver/subdiaphragmatic abscess, gross ascites or right lower-lung collapse; and abnormally low in cases with pushed down liver, e.g. in right pneumothorax or intestinal perforations (due to gas under diaphragm).
- *Coin test (Bell tympany)* is positive in massive pneumothorax or at the level of air-fluid interface in hydropneumothorax.

(***Coin test:*** Place a coin over the affected site and tap with other coin. A distinct metallic bell-like sound (hammer on an anvil) is audible directly or with stethoscope, on diametrically opposite side of chest wall).

IV. Auscultation is most informative and includes identification of—(a) character of breath sounds, (b) presence of adventitious sounds, (c) vocal resonance, and (d) other important signs.

- ***Breath sounds*** may be divided into—(a) vesicular, or (b) bronchial breathing.
  – *Normal vesicular breathing* with long inspiratory and shorter expiratory phase without intervening pause. In children, vesicular breathing is relatively harsh due to thin chest wall and bronchial character, discussed below, may be normally present over right apex and mid-scapular region.
  – *Abnormal Bronchial breathing* with—(a) equal duration of inspiratory and expiratory phase, and (b) an intervening pause between two phases.

    Bronchial breathing is usually heard over—(a) consolidation, (b) collapse with patent bronchus, (c) air-fluid level in effusion/hydropneumothorax due to collapsed lung, (d) cavity communicating with bronchus, and (e) communicating pneumothorax. Unlike adults, further differentiation of bronchial breathing into *tubular* (consolidation), *cavernous* (cavity) or *amphoric* (pneumothorax) types is neither easy, nor desirable in children.
  – Absence or reduced breath sounds indicate underlying collapse, effusion or pneumothorax.
- ***Adventitious sounds*** on auscultation include crepitations (rales), rhonchi, conducted sounds and Friction rub.
  – *Crepitations* are predominantly *inspiratory*, crackling/bubbling sounds due to presence of fluid in bronchi or alveoli. In crying children, crepitations are best audible in inter-cry phase, when baby takes a deep breath. Crepitations may be *fine* (crackling, due to fluid in alveoli) or *coarse* (bubbling, due to fluid in bronchi).

    Important causes of crepitations include: (a) Bronchopneumonia (coarse), (b) Bronchiectasis, cavity, lung abscess (coarse, bubbling), (c) Pulmonary edema (fine, inspiratory and mainly at bases), (d) Bronchiolitis, asthma (fine, diffuse and expiratory), (e) Interstitial lung diseases/fibrosis (fine, inspiratory).
  – *Conducted sounds* originate from upper airways and must be differentiated from crepitations on the basis of—(a) nearly similar character all over the chest, (b) change of character on coughing/crying, (c) presence in both inspiration and expiration. Similar sounds may also be heard on placing the stethoscope over nose.
  – *Rhonchi* are *expiratory* musical sounds, due to passage of air through narrowed airways. Rhonchi may be *sonorous* (low-pitched, in large airway obstruction) or *sibilant* (high-pitched, in smaller airway obstruction), often associated with audible wheeze. Rhonchi are common in—(a) asthma, (b) bronchiolitis, (c) pneumonia in young children, and (d) other causes of wheezing (Ch 16.4.4).
  – *Pleural rub* is a *crackling sound* due to friction of two pleural layers in pleurisy, before the appearance of fluid. Unlike crepitations, it is—(a) audible during inspiration as well as expiration, (b) accentuates on pressure from stethoscope, (c) localized usually in anterior axillary line, (d) not altered by coughing, and (e) disappears soon after collection of plural fluid. Pleural rub is frequently associated with chest pain during deep inspiration.
- ***Vocal resonance (VR)*** denotes audible laryngeal vibrations conducted via airway and lung (akin to palpatory TVF). Presence of a patent bronchus and conductive overlying media (lung tissue) is essential for VR.

  Clarity of vocal sounds depends on density of conductive media and may be further classified as *bronchophony* (sounds clear but words not identifiable), *whispering pectorilquy* (words identifiable) and *egophony* (nasal quality of sounds).
  – *VR is increased* in—(a) consolidation, (b) cavity communicating with bronchus (whispering pectoriloquy), (c) above the level of pleural effusion

or hydropneumothorax (egophony), (d) collapse with patent bronchus.
  - *VR is reduced* in—(a) pleural effusion/thickened pleura, (b) pneumothorax, and (c) collapse without patent bronchus, and (d) emphysema, due to poor conductivity of hyper-inflated lung.
- ***Other important auscultatory signs*** in respiratory disease include:
  - *Succussion splash*-a splashing-sound of fluid movements, heard over the lesion on shaking the patient, in hydropneumothorax, diaphragmatic hernia and rarely, large cavities.
  - *Post-tussive suction*-a sucking sound after coughing, due to sudden gush of air in large cavities, communicating with bronchus.

16.3 LABORATORY INVESTIGATIONS IN LUNG DISEASE

Important investigations in respiratory disorders include:
- Radioimaging, e.g. X-rays, CT/MRI, USG, etc. for anatomical localization of lesion and detection of fluids, etc.
- Pulmonary function tests and lung scintigraphy, for physiological assessment.
- Endoscopic studies, e.g. bronchoscopy or thoracoscopy, for direct visualization of pathology.
- Blood gas analysis for severity of disease (Ch 27.2)
- Microbiological or serological studies for etiological diagnosis.

Radioimaging studies: The choice of radioimaging study depends on clinically suspected pathology and site of lesion.

- **Chest X-rays:** Plain chest X-ray in PA and lateral view, preferably in erect position, is the baseline investigation for diagnosis and localization of pulmonary lesion. In addition, A *decubitus* film is indicated for suspected hydropneumothorax or fluid-filled cavity.

  Thorough evaluation of chest X-ray should include: (a) soft tissue/bony cage shadows, (b) position of trachea, (c) crowding/widening of intercostal spaces, (d) location, shape and size of cardiac silhouette, (e) mediastinal widening and *carinal angle*, i.e. bifurcation angle between two major bronchi (N: ~70–80°), (f) diaphragmatic contours (normally right is higher than left), (g) obliteration of costophrenic or cardiophrenic angles, (h) subdiaphragmatic abnormality, and *of course*, (i) the status of lung parenchyma with/without air bronchogram.

  Parenchymal lesions may be broadly classified as: (a) *diffuse or localized* (peripheral, perihilar, patchy, circular), (b) *hyperlucency or opacity* (homogenous or non-homogenous), and (c) *special characteristics*, e.g. shape, air-fluid levels, etc. **(Table 16.3)**.

TABLE 16.3: Radiological D/D of lung shadows

- **Diffuse, non-homogenous opacities**
  - Bronchopenumonia (large, confluent)
  - Miliary mottling (small, discrete, uniform)
  - Interstitial pneumonia
  - Pulmonary edema
- **Focal, homogenous opacities**
  - Consolidation (no tracheal shift)
  - Collapse, fibrosis (trachea on same side)
  - *P. effusion*, empyema (trachea on opposite side)
- **Solitary rounded shadows (with/without air)**
  - Tubercular cavity, lung abscess (thick walled)
  - Lung cysts, pneumatoceles (thin walled)
  - Encysted pyopneumothorax
- **Diffuse/localized hyperlucency**
  - Pneumothorax (trachea on opposite side)
  - Emphysema (no tracheal shift)
- **Localized multi-cystic hyperlucency**
  - Pneumatoceles
  - Bronchiectesis
  - Diaphragmatic hernia

*also *see* X-rays in Figs 16.11 and 10.4.

Other X-rays, e.g. paranasal sinuses (recurrent sinusitis), mastoid (chronic otitis media), neck (acute croup) are indicated in selected cases.

- **Ultrasonography (USG)** is very useful to detect small pleural effusions as well as during thoracocentesis. It is also emerging as *point of care* imaging of choice to detect and monitor pneumonia in intensive care units.
- **CT thorax** is most informative investigation for localization and monitoring of pulmonary, pleural and mediastinal lesions and has almost replaced need for bronchography and diagnostic bronchoscopy. It is mainly indicated in—(a) chronic lung diseases or (b) acute lung diseases with abnormal course, e.g. unresolving pneumonia or suspected abscesses, (c) cysts or other congenital malformations, and (d) for guided biopsy or aspiration of mediastinal lesions. ***CT sinus/mastoid*** is indicated in suspected sinusitis/mastoiditis.
- ***MRI*** is of limited value in parenchymal lung lesions, but more useful in suspected *vascular*, mediastinal or underlying spinal/bony lesions.
- **Fluoroscopy,** once frequently used to detect diaphragmatic paralysis and non-opaque foreign bodies, is rarely used now, due to risk of excessive radiation and availability of superior tests.

Pulmonary function tests (PFT) are of limited value in children due to lack of cooperation, though provide valuable insight to altered pulmonary physiology in cooperative cases.

Uses: PFT are valuable diagnostic aids to—(a) differentiate between obstructive *vs.* restrictive lung disease, (b) assess the severity of functional impairment, and (c) monitor the course of disease and response to therapy.

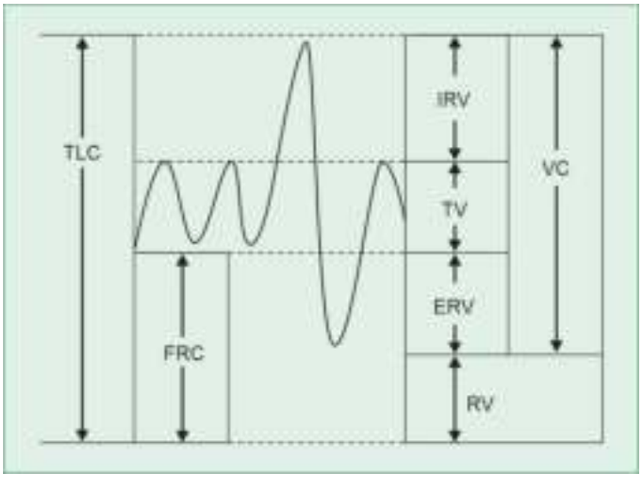


Fig. 16.3: **Static lung volumes.**
TLC: Total lung capacity; **FRC:** Functional residual capacity; **TV:** Tidal volume; **RV:** Residual volume; **IRV:** Inspiratory reserve volume; **VC:** Vital capacity; **ERV:** Expiratory reserve volume.

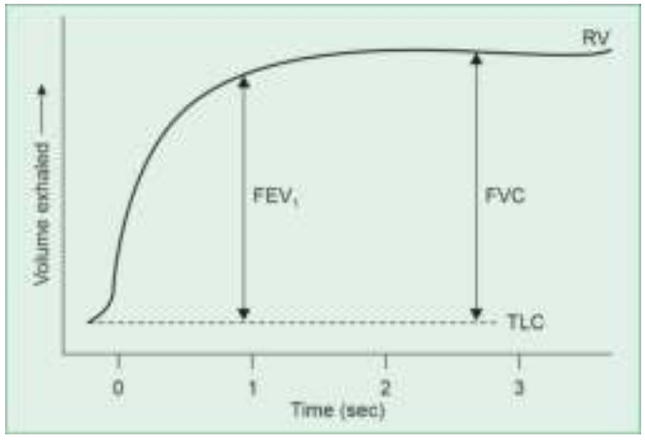


Fig. 16.4: **Kinetic lung volumes.**
TLC: Total lung capacity; **FVC:** Forced vital capacity; **FEV_1:** Force expiratory volume in 1 second; **RV:** Residual volume.

Principle: PFT involves study of:

- *Static lung volumes/capacities* **(Fig. 16.3)**, which are mainly altered in restrictive lung diseases, due to anatomical loss of parenchyma, reduced elastic recoil and/or restricted expansion of the lung. Functional vital capacity (FVC) is the most important static indicator of restrictive lung disorders.
- *Kinetic airflow rates* during different phases of breathing are mainly affected in obstructive airways diseases due to increased airway resistance. Two most important kinetic flow rates in practice include: *Forced vital capacity* (FVC) and *Forced expiratory volume in first second of expiration* (FEV_1) **(Fig. 16.4)**.
- *Flow-volume relationships* for comparative assessment of parenchymal (restrictive) or airway (obstructive) pathology. These relationships are studied on graphic flow-volume curves provided directly on spirometry or by calculating the ratios like FEV_1/FVC.

Methodology: PFT are recorded by a manual or computerized spirometer that provides a graphic record of lung volumes and flow rates during various phases of respiration. However, spirometer cannot measure the Residual volume (RV), which needs to be assessed by gas dilution/wash-out methods.

While rarely used in practice, body plethysmography is an alternative and more accurate method to determine lung capacities (including residual volume and airway resistance), specially in uncooperative patients.

Interpretation: Primary value of PFT lies in differentiating obstructive airway diseases from restrictive lung diseases **(Table 16.4)**.

Restrictive lung diseases include those with: (a) restrictive chest-wall, e.g. scoliosis, neuromuscular disorders, etc., (b) restricted alveolar expansion, e.g. pneumonia, pulmonary edema or high surface tension, e.g. ARDS, and (c) reduced elastic recoil, e.g. interstitial lung diseases or fibrosis. These diseases are characterized by:

- Predominant loss of lung volumes/capacities, i.e. reduced TLC, VC, RV and FRC,
- Near-normal flow rates, e.g. FEV_1, and
- Normal or even increased FEV_1/FVC.

TABLE 16.4: PFT in obstructive vs restrictive lung diseases

PFT Indices	*Obstructive*	*Restrictive*
FVC	↓/N	↓↓
FEV_1	↓↓	↓/N
FEV_1/FVC	↓ (80%)	N/↑

FVC: Forced vital capacity, **FEV_1:** Force expiratory volume in 1 second.

Obstructive lung diseases due to narrowed airways and increased airway resistance during expiration, e.g. asthma, emphysema or chronic bronchitis, etc. are characterized by:

- Predominant decrease in FEV_1.
- Minimum decrease in lung volumes. FRC is even increased in asthma due to air-trapping.
- Marked reduction in FEV_1/FVC.

Mid-maximal expiratory flow rate (MMEFR)—the average flow during the middle 50% of FVC, is more reliable indicator of mild airway obstruction before FEV_1 becomes abnormal, though difficult to record in children.

Asthma is further distinguished from other obstructive disorders by the *reversibility*, i.e. >15–20% increase in FEV_1 after salbutamol nebulization.

Peak flowmetry is a simple, reliable alternative to spirometry for regular monitoring of airway status in asthma, nearly comparable with FEV_1 (Ch 16.8 and 29.5).

Lung scintigraphy (radionuclide scan): Lung scintigraphy is rarely used to assess ventilation and/or perfusion status in different parts of the lung, after administration of a radiotracer agent. It is a safe and sensitive investigation for early detection of subtle lung dysfunction. Lung scans include-perfusion scans, ventilation scans and mixed scans.

Perfusion scan involves IV administration of a radiotracer (^{99m}Tc MHSA), which gets trapped into the pulmonary vascular bed in proportion to the regional blood flow. Subsequent radioimaging of different parts of lungs provides information regarding perfusion abnormalities.

Ventilation scan is performed after inhalation of a radioactive gas (^{133}Xe), followed by serial radioimaging to study its clearance (wash-out) from the lungs. Inadequately ventilated parts of the lungs show delayed appearance or clearance of radioactivity on serial images.

Combined ventilation-perfusion scan are obtained by IV administration of ^{133}Xe, followed by serial radioimaging to note the rate of appearance and disappearance of the tracer in the lungs. Appearance of radiotracer in the lung after injection is a measure of perfusion, whereas its clearance indicates ventilatory status.

Important lung scintigraphic abnormalities include:

- *Predominantly perfusion abnormalities* in pulmonary embolism, AV malformations and interstitial lung diseases, etc.
- *Predominantly ventilatory abnormalities* in foreign body, lung sequestration/hypoplasia, diaphragmatic hernia, etc.
- *Combined ventilation-perfusion abnormalities* in chronic obstructive airway disorders, e.g. asthma.

Diagnostic value of these lung scans is limited due to *lack of specificity*. However, new-generation lung scans, e.g. Gallium scan (^{67}gallium), positron emission tomography (PET) and single photon emission computed tomography (SPECT)-a scintigraphic analogue of CT scan, are useful in early diagnosis and monitoring of chronic, slowly progressive lung diseases.

Bronchoscopy is a very useful diagnostic as well as therapeutic procedure to: (a) visualize the trachea lumen and larger bronchi, (b) collect specimens for cytological and microbiological studies, e.g. biopsy, bronchoalveolar lavage (BAL), and (c) remove foreign bodies, etc.

Indications for bronchoscopy include:

- *Diagnostic*
  - Foreign body, congenital anomalies or mass lesions
  - Persistent cough, stridor, wheeze or hemoptysis
  - Recurrent/persistent pneumonia, collapse, emphysema
  - Bronchoalveolar lavage and endobronchial biopsy
- *Therapeutic*
  - Removal of foreign body or mucus plugs
  - Dilatation of tracheo-bronchial strictures
  - Resection of endobronchial mass lesions
  - Bronchial toilet in suppurative lung diseases
  - Endobronchial drug instillations

Methodology: Bronchoscopy is done under general or local anesthesia using a rigid or flexible fiberoptic bronchoscope. Rigid scope is preferred for foreign body removal, endoscopic mass resection and in presence of heavy hemoptysis, while flexible bronchoscopy is preferred in other cases due to ease of manipulation and more distal reach. Bronchoalveolar lavage (BAL) is collected by sequential instillation and withdrawal of sterile saline.

Complications of bronchoscopy include: (a) sudden reflex laryngospasm, (b) subglottic edema, (c) trauma, e.g. bleeding or pneumothorax, (d) nosocomial pneumonia, and (e) anesthesia-related complications.

Thoracocentesis is a common diagnostic/therapeutic procedure to access pleural fluid in effusions/empyema. A 16–18 g. Needle is inserted along the *upper edge of lower rib in 7th or 8th ICS in posterior axillary line* (sitting position) or under USG guidance with proper aseptic precautions and local anesthesia (Ch 32.6). Total aspirated volume in single sitting should not exceed >5% of body weight.

Common complications include—(a) pneumothorax, (b) infection, and (c) traumatic puncture of liver/spleen or bleeding, and rarely, (d) sinus/fistula formation (in tubercular effusion).

Percutaneous lung aspiration is rarely used, to collect parenchymal specimen for bacteriological studies in non-resolving pneumonia. After radiological localization of lesion, a needle attached to a saline-filled syringe is inserted and advanced to the site of interest > the saline is injected > re-aspirated quickly, to collect a few drops of parenchymal specimen, and > the needle is withdrawn. Pneumothorax is a common complication of this procedure.

Lung biopsy is rarely used in children to establish the diagnosis of chronic non-infectious lung disorders, e.g. interstitial lung disease or lymphocytic interstitial pneumonitis in HIV infected children. It may be performed via a bronchoscope, though USG-guided or thoracoscopic biopsies are preferred in young infants to ensure adequate sample size.

16.4 COMMON CLINICAL PRESENTATIONS

16.4.1 RECURRENT/PERSISTENT COUGH

Cough is a protective reflex to expel mucus or noxious substances, e.g. foreign body, dust, fumes and infectious agents from air passage by *sudden and forceful expiration against partially closed glottis*.

Cough reflex arc includes—(a) *afferents* from airways (pharynx to second-order bronchi), pleura, and ears,

(b) central *cough center* in medulla, and (c) *efferents* to laryngeal and respiratory muscles.

While acute cough is generally benign or self limiting, recurrent/persistent cough, though ill defined, needs detailed evaluation.

Etiology: Common causes of recurrent/persistent cough include—(a) *infective*, (b) *allergic*, (c) *anatomical or* obstructive, and (d) *psychogenic* or habit cough.

a. ***Infective cough*** is usually, but not always, associated with fever and indicates recurrent/persistent respiratory infections (RRTI/PRTI). RRTI generally refers to three or more documented attacks over 6 months, while PRTI denotes persistence of infection for > 4 weeks, despite treatment. Etiologically, RRTI/PRTI may be due to environmental causes (re-infection from external source) due to re-activation/persistence of underlying pathology **(Table 16.5)**.

b. ***Allergic cough*** may be due to *intrinsic nasobronchial allergy*, e.g. asthma, allergic rhinitis or *environmental factors*, e.g. air pollution, passive smoking, etc. Allergic cough is typically paroxysmal, wheezy and associated with positive family or environmental history.

c. ***Anatomical or obstructive cough*** is frequently laryngotracheal in origin, due to congenital or acquired airway abnormalities, e.g. foreign body, adenoids, etc. Cough is typically *brassy or barking*, stridor is common and most cases present in early infancy or toddler age group.

d. ***Habit cough*** is common in older children, often as a residual lingering symptom after an attack of respiratory illness, which is typically—(a) refractory to treatment, (b) absent during sleep and when the child is unsupervised, and (c) without physical signs.

TABLE 16.5: Risk factors for RRTI/PRTI

- **Environmental**
  - *Overcrowding:* Slums, orphanages
  - Cross-infection in family/school
- **Airway pathology**
  - ***Recurrent aspiration***
    Congenital anomalies: Cleft palate, TEF (H type)
    Neuromuscular: GER, C. Palsy, Down syndrome
    Top feeding
  - ***Airway obstruction***
    Upper: Adenoids, nasal polyp
    Lower: Asthma, mediastinal nodes, foreign body
  - ***Defective mucociliary clearance***
    Kartagener syndrome, cystic fibrosis
    Vitamin A deficiency
- **Chronic lung diseases**
  - Tuberculosis, bronchiectesis, pertussis
  - Partially-treated bacterial pneumonia
  - Underlying lung cysts/hypoplasia
- **Increased pulmonary vascularity**
  - Pulmonary hypertension, e.g. in CHDs, RHD
  - Chronic renal disease (fluid overload)
- **Immunodeficiency states**
  - *Secondary:* AIDS, PEM, steroid therapy
  - Primary immunodeficiency disorders
- **Others**
  - *Allergic:* Asthma, allergic rhinitis
  - Vasomotor rhinitis or rhinitis medicamentosa
  - *Pollution:* Environmental, passive smoking

TEF: Tracheoesophageal fistula; **GER:** Gastroesophageal reflux

Diagnostic evaluation for recurrent/persistent cough or RRTI/PRTI includes:

- ***Detailed history*** regarding:
  - *Age of onset:* Recurrent/persistent cough in early infancy indicates possible congenital anomaly, e.g. H-type tracheoesophageal fistula (TEF) or gastroesophageal reflux disease (GERD) while foreign body and pertussis are common in toddlers. Asthma, tuberculosis and suppurative lung diseases are common beyond older children.
  - *Character:* Paroxysmal cough indicates asthma, pertussis and foreign body. Cough may be *dry and hacking* (URTI), *brassy/barking* (croup, habit cough), *staccato* (chlamydia) or *hawking/throat clearing* (post-nasal drip). *Wet productive cough* indicates parenchymal (pneumonia, bronchiectasis) or distal airway disorders (asthma, bronchitis).
  - *Sputum* is *mucoid* in asthma, *purulent* in bronchiectasis or lung abscess and *blood-stained/rusty* in pneumococcal pneumonia, foreign body, pertussis, bronchiectasis, tubercular cavity or mitral stenosis. Frank hemoptysis is uncommon, except due to cavitary tuberculosis in older children/adolescents.
  - *Diurnal/postural variations*, e.g. *morning* cough (asthma, bronchiectasis), *late-night* cough (post-nasal drip, asthma, CCF), or cough *bouts after change of posture* (bronchiectasis, abscess).
  - *Presence of abnormal sounds*, e.g. *snoring* (adenoids), *stridor* or rattling (laryngotracheal lesion), *wheeze* (asthma). Presence of *grunt* is a bad prognostic sign, indicating severe distress.
  - *Associated symptoms*, e.g. fever (infective), exertional dyspnea (exercise-induced asthma or cardiac disease), persistent rhinorrhoea (adenoids, nasal polyp), sneezing (allergic rhinitis), etc.
  - *Family history* of atopic disorders or contact with tuberculosis.
  - *Past history* of sudden choking (foreign body) or similar episodes with treatment details.
  - *Environmental history* suggestive of overcrowding, air pollution and passive smoking
  - *Dietary history*-Top-fed infants are more susceptible for RRTI than breast-fed babies.
- ***Clinical examination,*** including:
  - *General examination,* specially for failure to thrive, clubbing (bronchiectasis, lung abscess) and central cyanosis (cardiac pathology), etc.

TABLE 16.6: Common cough remedies

Cough suppressants	**Mucokinetic agents**
(Dry, non-asthmatic cough)	*(Asthmatic cough)*
Codeine*	Guaiphenesin
Dextromethorphan	Ipecacuanha
Noscapine	Ammonium chloride
Pholcodine	Na/K citrate
Antihistaminics	**Mucolytics**
(Acute allergic cough)	*(Asthmatic cough)*
Chlorpheniramine	N-acetylcysteine
Diphenhydramine	Bromhexine
Decongestants	Ambroxol
(Rhinorrhea, post-nasal drip)	Carbocysteine
Pseudoephedrine	
Phenylephrine*	
Phenylpropanolamine*	

*To be avoided in children

TABLE 16.7: Causes of acute respiratory distress

- **Respiratory causes**
  - *Upper airway:* Diphtheria, croup, foreign body
  - *Lower airway:* Bronchiolitis, asthma
  - *Pulmonary:* Pneumonia
  - *Pleural:* Empyema, pneumothorax
- **Cardiovascular diseases (pulmonary edema)**
  - Congenital heart diseases
  - Pericardial effusion
  - Myocarditis/myocardiopathy
- **Neurological disorders**
  - *CNS:* Meningitis, encephalitis
  - *Neuromuscular:* Poliomyelitis, Guillain Barré syndrome
- **Metabolic acidosis**
  - Diabetic ketoacidosis
  - Renal tubular acidosis
  - Dehydration
- **Poisonings,** e.g. salicylate poisoning

  - *ENT examination* to exclude local nasopharyneal pathology, adenoids and post-nasal drip. Periorbital puffiness or sinus tenderness indicates sinusitis.
  - *Chest examination* to identify the type and location of pulmonary lesion
- ***Relevant investigations,*** including:
  - *Baseline investigation*, e.g.
    - Blood counts for leukocytosis, eosinophilia
    - X-ray chest and sinuses
    - Tuberculin test
    - Sputum examination
    - Pulmonary function tests, to exclude asthma
  - *Selected investigations*, e.g.
    - CT/HRCT
    - Milk scan to exclude GERD and H-type TEF.
    - Bronchoscopy with bronchoalveolar lavage
    - Sweat chloride test for cystic fibrosis
    - Microbiology/serology including HIV test
    - Lung biopsy in very rare cases

Management of recurrent/persistent cough depends on the identified etiology.

Non-specific cough remedies **(Table 16.6)** for symptomatic relief, though frequently used in practice, are often not required. However, if necessary, single drug preparations should be preferred than irrational multidrug combinations, with following principles:

- *Acute cough/coryza*: Antihistaminic + Decongestant
- *Persistent dry/irritating cough*: Cough suppressants.
- *Persistent wet cough/asthma*: Mucolytics or mucokinetics.

16.4.2 RESPIRATORY DISTRESS

Respiratory distress (RD) is a medical emergency suggestive of underlying hypoxia and compensatory ventilatory efforts.

Clinical indicators of RD, in order of progressive severity include: (a) tachypnea, (b) labored breathing, i.e. inter-/subcostal indrawing, nasal faring and use of accessory muscles, (c) cyanosis, (d) air hunger with altered sensorium, and terminally, (e) respiratory failure.

Etiology: While RD is a sign of innumerable respiratory and extra-respiratory pathologies **(Table 16.7)**, acute respiratory infections and asthma are two dominant causes in children, together accounting for >80% cases.

Diagnosis: Etiological diagnosis depends on: (a) age of onset, (b) duration, onset and course of RD, (c) coexisting symptoms, (d) clinical examination (not limited to respiratory system only) and relevant investigations. Chest X-ray is mandatory in all cases, even in absence of clinical findings.

Management: All children with RD, irrespective of cause and severity need to be hospitalized immediately, followed by oxygen supplementation and ventilatory assistance as required. For further details, *see* Ch 27.2 on acute respiratory failure.

16.4.3 STRIDOR

Stridor is a harsh, medium-pitched *inspiratory* sound due to obstruction of upper airways, i.e. larynx and extrathoracic trachea. However, stridor of tracheal obstruction may be biphasic or predominantly expiratory in nature.

Stridor is common in infants even with minor infections, due to smaller larynx, rigid cricoids cartilage and loose submucous connective tissue around glottic region. However, onset of acute stridor in a previously well child indicates life-threatening emergency.

Etiology: Acute infectious croup and foreign body are two most common causes of stridor beyond infancy, while its presence in newborn indicates congenital airway anomalies, e.g. laryngomalacia or congenital subglottic stenosis **(Table 16.8)**.

TABLE 16.8: Causes of stridor

Acute stridor
- *Infections:* Diphtheria, acute infectious croup
- Foreign body inhalation
- *Allergic* - anaphylaxis, angioneurotic edema
- Hypocalcemic tetany (laryngismus stridulus)
- *Psychogenic:* Hysteria

Persistent/Recurrent stridor
- *Developmental:* Laryngomalacia
- *Oro-facial:* Choanal atresia, Pierre Robin syndrome
- *Extrinsic airway compression:*
  - Quinsy, retropharyngeal abscess etc.
  - Mediastinal tumors or lymph nodes
  - Pulmonary lobar emphysema, lung cysts
  - Retrosternal thyroid/goiter
- *Intrinsic airway obstruction:*
  - Congenital webs, stenosis or clefts
  - Tumors, e.g. papillomas
  - Post-tracheostomy stenosis
- *Neurological:* Unilateral vocal cord palsy

TABLE 16.9: Causes of wheezing

- **Hyper-reactive airway disorders (HRADs)**
  - Bronchial asthma
  - Acute bronchiolitis
  - Post-infectious wheeze (in infants)
  - Tropical pulmonary eosinophilia (TPE)
  - Loeffler syndrome
  - Environmental exposure to dust, smoke etc.
  - *Others* - aspergillosis
- **Chronic broncho-pulmonary disorders**
  - *Aspiration pneumonia:* GERD, H-type TEF
  - Bronchopulmonary dysplasia
  - Bronchiolitis obliterans
- **Endo-bronchial/tracheal lesions**
  - Foreign body/aspiration
  - Endobronchial tuberculosis
- **Extrinsic airway compression**
  - Mediastinal tumors, nodes
  - Aberrant mediastinal vessels
- **Miscellanoeus:** CCF, hysterical wheezing

Diagnostic evaluation in stridor includes:
- ***Detailed history,*** related to:
  - *Age of onset:* Stridor is present since birth in congenital anomalies, while laryngomalacia manifests after 2–3 weeks. Infections and foreign body inhalation are more common in older infants and children.
  - *Course:* Persistent stridor indicates congenital anomalies or foreign body. In laryngomalacia, stridor gradually improves with advancing age.
  - *Associated symptoms*, e.g. barking/brassy cough or hoarse cry (croup, vocal cord palsy), drooling of saliva (epiglottitis, foreign body, quinsy), snoring (adenoidal hypertrophy), dysphagia (supraglottic lesion) and fever (infective croup, quinsy).
  - *Worsening factors*, e.g. crying or supine position (laryngomalacia, macroglossia), during night (croup), after feeding (H-type TEF).
  - *Past history* of upper respiratory infection (Croup), choking spells (foreign body, TEF), endotracheal intubation (vocal cord palsy, tracheal stenosis).
  - *Concomitant illness*, e.g. atopy (angioneurotic edema, spasmodic croup), psychogenic disorders (hysteria).
- ***Clinical examination,*** specially for-
  - *Facial dysmorphism* (congenital airway anomalies)
  - *Expiratory stridor* (subglottic or tracheal lesions)
  - *Throat examination* for membranes (diphtheria), cherry-red epiglottis (acute epiglottitis), etc. Throat examination should be deferred till resuscitative measures are available, in suspected acute epiglottitis, due to risk of sudden laryngospasm and death.
- ***Relevant investigations*** include:
  - *X-ray of neck* (AP/lateral) to show *Steeple sign*, i.e. narrowed tracheal air-column in the subglottic stenosis or *Thumb sign* in epiglottitis.
  - *CT/MRI of neck* and chest for extrinsic lesions, e.g. retropharyngeal abscess, mediastinal mass. Virtual bronchoscopy may help to detect foreign bodies in airways.
  - *Laryngo/bronchoscopy* in persistent stridor, which is also to be used for removal of obstruction.
  - *Other investigations* in select cases, e.g. esophagoscopy, to exclude external pressing lesions.

16.4.4 WHEEZING

Wheezing indicates *expiratory airway obstruction*, usually at the *distal bronchial or bronchiolar level*, due to bronchospasm, mucosal edema and/or excessive mucus production. Young children are more susceptible for wheezing due to narrower airways. Rhonchi, the auscultatory equivalent of wheeze, are almost invariably present.

Etiology: Bronchial asthma and acute bronchiolitis are commonest causes of recurrent and non-recurrent wheezing, respectively **(Table 16.9)**. Unlike adults, infants may also wheeze during lower respiratory tract infections, e.g. pneumonia, due to transient airway hypersensitivity and narrower bronchial lumen.

Diagnostic evaluation in a wheezy child includes:
- ***Detailed history,*** specially related to:
  - *Age of onset:* Wheezing in early infancy is most likely due to bronchiolitis or pneumonia. Asthma rarely manifests before 6 months of age.
  - *Similar preceding attacks* indicates asthma, though tropical eosinophilia, GER and H-type TEF should also be excluded.
  - *Past history* of viral upper respiratory infection (bronchiolitis), asthma, aspiration (GER, H-type TEF), helminthiasis (tropical eosinophilia).
  - *Family history* of atopic disorders (asthma).

TABLE 16.10: Causes of hemoptysis

- **Infections**
  - *Acute:* Pneumococcal pneumonia (rusty sputum)
  - *Chronic:* TB, lung abscess, bronchiectesis
- **Vascular**
  - Pulmonary hypertension, e.g. mitral stenosis (frothy)
  - AV malformations of lung/bronchi
- **Traumatic**
  - Chest-wall injury/bronchial foreign body
  - Post-surgery/bronchoscopy
- **Bleeding disorders:** DIC (pulmonary hemorrhage)
- **Others:** Lung cysts/tumors, Goodpasture syndrome

TABLE 16.11: D/D hemoptysis vs hematemesis

	Hemoptysis	***Hematemesis***
Color	Bright red	Dark red/brown
pH	Alkaline	Acidic
Other contents	Frothy sputum	Food particles
Asso. symptoms	Cough/dyspnea	Vomiting/nausea
Lung signs	Present (crepts)	Absent
Evidence of…	Lung disease	GIT/liver illness

  - *Environmental history* of air pollution or passive smoking (allergic, asthma).
- ***Clinical examination,*** *specially for:*
  - Growth failure (asthma, chronic lung disease),
  - ENT checkup to exclude allergic rhinitis,
  - Chest findings, including character of rhonchi,
  - Signs of congestive cardiac failure.
- *Relevant investigations:*
  - *Blood:* Eosinophilia, IgE levels (allergic)
  - *Nasal discharge smear:* Eosinophils (allergic)
  - Pulmonary function tests for asthma
  - X-ray chest/sinuses to exclude infections
  - Milk scan to exclude H-type TEF fistula and GERD
  - Other relevant tests, especially for allergy

Important differences between two most common causes of wheezing in childhood, i.e. bronchial asthma and acute bronchiolitis are given in **Table 16.17**.

Other uncommon presentations of respiratory diseases in children are as follows:

Hemoptysis, i.e. *expectoration of blood or blood-mixed sputum* is uncommon in childhood **(Table 16.10)** and must be differentiated from more common hematemesis **(Table 16.11)** *or* spitting of swallowed blood in epistaxis.

Management of hemoptysis include: (a) immediate supportive therapy with airway suction, oxygen supplementation, blood transfusions and vasopressors, e.g. IT epinephrine or IV pitressin infusion followed by, (b) bronchoscopy to embolize bleeding vessel, if identified, and (c) treatment of primary cause.

Chest pain is a common but usually a benign complaint in childhood due to multiple causes **(Table 16.12)**.

TABLE 16.12: Causes of chest pain

Chest-wall related: *(commonest)*
- *Trauma:* Accidents, heavy exercise
- *Inflammatory:* Costochondritis, herpes-zoster
- Compressive myelopathy

Pulmonary
- *Pleural:* Pleurisy, pleurodynia, pneumothorax
- Severe/persistent cough or dyspnea, e.g. asthma
- *Rare:* Pulmonary infarction, tumors

Gastrointestinal
- Esophagitis, e.g. in GERD, acid peptic disease
- Sub-diaphragmatic abscess

Cardiovascular
- Pericarditis
- *Coronary:* Aortic stenosis, Kawasaki disease
- *Others:* Mitral valve prolapse, cardiomyopathies

Psychiatric
- Anxiety or panic disorder
- Attention-seeking behavior

Diagnosis is usually obvious on clinical evaluation, e.g. (a) location of pain, (b) relation with respiration, exercise or posture, (c) history of preceding trauma/infection, and (d) associated signs of musculoskeletal, respiratory or cardiac disease, supported by relevant investigations.

Presence of syncope, dyspnea or irregular pulses along with chest pain indicates possibility of a significant cardio-pulmonary disease.

Hiccups, i.e. *frequent, rhythmic clonic contraction of diaphragm* is a common but generally benign and self-limiting problem. Persistent hiccups may be due to:
- *Phrenic nerve/diaphragm irritation*, e.g. in basal pleurisy/pneumonia, GERD, mediastinal tumors, etc.,
- *CNS disorders*, e.g. head injury or posterior fossa lesions, and
- *Systemic causes*, e.g. uremia or alcohol intoxication.

Occasionally, acute hiccups may be caused by presence of a foreign body in ear, due to vagal stimulation.

Physiological measures, e.g. breath-holding and pharyngeal stimulation are effective in most cases, though severe intractable cases may need medical therapy with haloperidol or metoclopramide and treatment of primary cause.

16.5 EAR, NOSE AND THROAT DISORDERS

Upper respiratory tract spans from nose to oropharynx and related structures, e.g. paranasal sinuses and ear, which provides first line of defence against inhalant challenges.

Upper respiratory tract infections (URTI) account for over half of the outdoor consultations in pediatric practice. Pathologies in these structures are often interrelated and generally clubbed together as ENT (ear, nose and throat) disorders.

16.5.1 NASAL DISORDERS

Nose provides for—(a) initial warming and humidification of inspired air, (b) filtration of large suspended particles (>6 μ), (c) mechanical microbial clearance by forward ciliary movements in nasopharynx and (d) immunological defence by secretary IgA and lysozymes in nasal secretions.

Choanal atresia is the commonest congenital malformation of the nose (1:7000), characterized by unilateral or bilateral, bony (90%) or membranous septum, between nose and pharynx. Other congenital anomalies are present in ~50% cases, including CHARGE syndrome (*c*oloboma of eye, *h*eart anomalies, *a*tresia choanae, *r*etarded growth/*r*enal anomalies, *g*enital and *e*ar anomalies).

Clinically unilateral atresia is often asymptomatic, except unilateral nasal discharge and stuffiness. However, bilateral choanal atresia present at birth with breathing difficulties and cyanosis specially during feeding, as newborns are obligatory nose breathers.

Diagnosis is suggested by: (a) failure to pass a catheter beyond the posterior nares, (b) *spatula test* for unilateral lesions, i.e. absence of steam vapors on affected side when a shining steel tongue depressor is kept in front of nares, and (c) lateral skull radiographs with a contrast medium instilled in the nostrils. CT/MRI studies are recommended to delineate bony anatomy before surgery.

Treatment: Bilateral choanal atresia needs immediate surgery in neonatal period with perforation/dilatation of *membranous lesions or* transnasal resection with stenting in *bony lesions,* after initial stabilization with oral airway or tracheostomy. Correction of unilateral atresia may be deferred for many years.

Acute rhinitis (common cold) is the commonest infection in childhood, with ~3–8 attacks per childhood years.

Etiology: Common cold is a viral illness, predominantly caused by—(a) rhinoviruses in 1/3rd cases, (b) coronaviruses, and (c) respiratory syncytial viruses. Last one frequently also involves lower airways with longer clinical course. Bacterial superinfection is not uncommon.

Incidence of rhinoviral infections is higher in—(a) preschool children, (b) winter season, (c) overcrowded slums/day-care centres, (d) passive smokers and (e) air pollution due to domestic smoke, vehicular or industrial emissions.

Pathogenesis: All common cold viruses are transmitted via droplets, close physical contact and fomites. Offending virus invades upper airway epithelium leading to release of chemical mediators (nasal itching) vascular edema with exudation (rhinorrhoea/stuffiness) and bronchoconstriction (cough). Sometimes, infection may spread downwards to cause sore throat, croup or bronchiolitis.

Strain-specific immunity develops within a week, mainly involving secretary IgA, with recovery. Subsequent infections are caused by different strains.

Clinical manifestations begin after 2–5 days of incubation period with *local symptoms*, e.g. acute rhinorrhoea, sneezing, nasal block, conjunctival congestion, mild cough or sore throat, etc., with or without *systemic symptoms,* e.g. fever, headache and bodyache.

Young infants may have feeding difficulties and disturbed sleep due to nasal obstruction. Night cough is common due to post-nasal drip. Nasal discharge is initially watery, but thickens gradually due to shedding of epithelial cells and leukocytes. Purulent discharge indicates secondary infection. Course is self-limiting with recovery in 5–7 days.

Common *complications* include: (a) otitis media, (b) sinusitis, (c) pneumonia, (d) croup, (e) triggering of asthma.

Diagnosis is clinical and cultures or serology is rarely indicated.

Treatment is symptomatic with—(a) plenty of oral fluids, (b) saline nasal drops to clear stuffy nose, (c) steam inhalation and (d) pharmacotherapy with antipyretics, antihistaminics and decongestants. Antibiotics do not affect the course, unless secondary infection is present.

Vitamin C and zinc, commonly claimed to be *cold-preventors*, are of doubtful value. Currently, no effective vaccine is available.

Allergic rhinitis is a common atopic disorder in children, characterized by *seasonal or perennial attacks of sneezing, rhinorrhoea and nasal stuffiness.*

Pathogenesis: Like other allergies, allergic rhinitis is also associated with—(a) inherent or acquired hyperresponsiveness of nasal mucosa, and (b) IgE mediated hypersensitivity on exposure to inhalant allergens, e.g. pollens, dust, danders, molds, etc.; leading to mucosal congestion, edema and excessive mucus secretion.

Clinically, allergic rhinitis may present with seasonal or perennial attacks, most intense during first 4–5 years of age. Family history of atopy is present in ~1/4th cases.

Acute attacks present with sudden onset of sneezing, profuse watery/mucoid rhinorrhoea, nasal stuffiness and itching sensation in nose, pharynx and ears. Conjunctival redness, itching and tearing may also be present.

After recurrent attacks, child may develop: (a) certain mannerisms, e.g. frequent wrinkling, i.e. *rabbit nose*, or rubbing of nose, i.e. *allergic salute*, (b) horizontal creases over nose, i.e. *Dennie's lines*, (c) creases on lower eyelids, i.e. Dennie-Morgan folds, (d) periorbital puffiness or dark circles, i.e. *allergic shiners*, and (e) Allergic *gape* with continuous open-mouth breathing.

Local examination may reveal bluish or pale nasal mucosa with mucoid discharge, hypertrophic pharyngeal follicles and post-nasal drip. Recurrent episodes may

lead to development of *nasal polyps, atrophic rhinitis, sinusitis* or *otitis media.*

Classification: Presently, AR is classified as—(a) *mild intermittent, (b) mild persistent, (c) moderate to severe intermittent, and (d) moderate to severe persistent*, based on the frequency of attacks as *intermittent* or *persistent* (symptoms for </> 4 days/week for more than 4 weeks) and severity of the attack as *mild or moderate-to-severe* (with disturbed sleep, school performance or daily activity).

Many cases have associated complications or comorbidities, e.g. conjunctivitis, sinusitis, otitis, adenoids, eczema and asthma. Children with AR have thrice higher risk of asthma.

Diagnosis is mainly clinical, supported by: (a) family history, (b) presence of eosinophils in nasal secretions, and (c) eosinophilia with raised IgE levels.

Identification of precipitating allergen is neither easy nor necessary in all cases, though may be possible in some older children by history, *in vivo* skin testing or *in vitro* Specific IgE estimation by serum immunoassays (Ch 8.4.1). Skin tests are negative in first few years of life due to sensitization confined to nose and sinuses.

D/D includes other causes of recurrent or persistent rhinorrhea including: (a) recurrent viral infections, (b) vasomotor rhinitis, (c) rhinitis medicamentosa, (d) nasal foreign body, and (e) anatomical causes, e.g. deviated nasal septum, nasal polyps, etc.

Vasomotor rhinitis is triggered by internal events, e.g. exercise, cold/heat exposure, strong odors, while *rhinitis medicamentosa* is caused by over-use of topical decongestants.

Management includes treatment of acute attacks and prevention of recurrent attacks.

- ***Acute attacks*** may be treated by *oral antihistamines*, preferably second-generation long-acting less-sedating cetirizine, fexofenadine or loratadine. Intranasal antihistamines (INAH) can be used in older children >6 years, though generally not preferred due to bitter trickle-down taste and somnolence. Topical decongestants, e.g. xylometazoline may be used briefly for nasal obstruction but should be avoided due to rebound congestion and risk of rhinitis medicamentosa.
- ***Prevention of attacks*** needs *intranasal steroids (INS)* with low systemic bioavailability as sprays in minimum possible doses, e.g. mometasone or fluticasone (50–100 µg/nostril OD in morning). Systemic steroids are rarely required.

Leukotriene-modifying agents (LTRA), e.g. Montelukast, have a modest effect on rhinorrhea and nasal blockage and can be used in selected cases.

Other preventive measures include: (a) *avoidance of allergen* exposure, e.g. dust, fumes and smokes, (b) *topical mast-cell inhibitors*, e.g. cromolyn sodium nasal spray on long-term basis, and (c) *immunotherapy for* desensitization against identified allergen, though rarely useful.

TABLE 16.13: Step-wise management of allergic rhinitis

Severity of disease	*Intervention*
Mild-intermittent	PO Antihistamines SOS
Mild persistent	PO Antihistamines + INS or LTRA
Moderate to severe intermittent	INS +/-INAH + LTRA + immunotherapy
Moderate to severe persistent	Nasal saline irrigation + + INS + LTRA + immunotherapy ? Ipratropium nasal spray

For abbreviations, see text

A step-wise approach is recommended by ARIA (allergic rhinitis and its impact of asthma) guidelines 2019, for management of allergic rhinitis **(Table 16.13)**.

Nasal polyps are benign pedunculated tumors of chronically inflamed mucosa, seen in-chronic sinusitis, allergic rhinitis and cystic fibrosis. These polyps often originate in middle meatus and present with persistent rhinorrhea, hyponasal speech, mouth-breathing and grape-like glistening-gray masses on rhinoscopy. Prolonged use of local decongestants and steroid spray may reduce the size of polyp, though surgery is needed in some cases.

Nasal foreign bodies, e.g. grains or peanuts, are common in toddlers, which may present immediately after lodgement *or* after many days with unilateral foul-smelling discharge, swelling and noisy breathing. Local trauma, aspiration and rarely tetanus are potential complications.

Easily visible foreign body may be removed by forcible blowing of nose or manually by forceps, suction or Katz catheter, if necessary after instillation of a topical decongestant to reduce the edema.

However, sharp, embedded or posteriorly located bodies need removal by ENT surgeon under rhinoscopic guidance. Blind attempts should be avoided due to the risk of pushing them further or aspiration.

Epistaxis (nose-bleed) is a common problem in childhood, especially in dry hot weather.

Etiologically, local trauma due to nose-picking or foreign body is the commonest cause of epistaxis **(Table 16.14)**, with bleeding from *Kiesselbach's plexus (Little area)* in anterior septum. Epistaxis from posterior septum or during sleep may lead to mild hematemesis/melena.

TABLE 16.14: Causes of epistaxis

- *Local trauma:* Nose picking, foreign bodies
- *Infections:* Acute rhinitis/sinusitis
- Allergic rhinitis
- *Vascular:* Telangiectasia, varicosities
- *Nasal growths:* Polyps, hemangioma
- *Systemic:* Bleeding disorders, leukemia*
- Hypertension

*specially promyelocytic type

Management of acute epistaxis includes: (a) local pinching of nose, (b) cold compresses, and (c) forward tilting of head to avoid tricking of blood in posterior pharynx, and (d) topical decongestants, e.g. xylometazoline. Nasal packing for few hours is required in some cases.

After control of bleeding, local examination helps to identify bleeding site, which may be cauterized with 1% silver nitrate. Children with recurrent epistaxis should be evaluated for systemic causes or posterior septal mass.

16.5.2 SINUSITIS

Paranasal sinuses are air-filled cavities within the facial bones, lined by ciliated, mucus secreting epithelium. The frontal, maxillary and anterior ethmoidal sinuses drain in middle meatus, while posterior ethmoidal cells and sphenoidal sinus drains into superior meatus.

Paranasal sinuses are not well developed at birth. While small ethmoidal and maxillary sinuses are present at birth, sphenoidal and frontal sinuses are not pneumatized till 9–10 months and 7–8 years of age respectively.

Sinusitis, i.e. inflammation of sinuses, frequently coexists with rhinitis (Rhinosinusitis) and may be acute or chronic (>30 days) with intermittent exacerbations.

Etiopathogenesis: Anatomical position of sinus ostia and mucociliary clearance are main defence mechanisms against sinus infection. Chronic sinusitis is more common in cases with:

- *Blocked sinus ostia* due to septal deviation, foreign body, polyps, adenoid hypertrophy etc.
- *Impaired mucociliary clearance* due to viral or allergic rhinitis, environmental pollution, immotile cilia syndrome, cystic fibrosis, etc.
- *Increased risk of infection*, e.g. gastroesophageal reflux, immunodeficiency states, etc.

Microbially, acute sinusitis is usually caused by *S. pneumoniae, H. influenza, Moraxella* and *Staph. aureus,* while polymicrobial and anaerobic infections are common in chronic disease. Fungal sinusitis is rare in immunocompetent children.

Clinical manifestations include: (a) persistent cough and nasal discharge that worsens in supine position, (b) headache, specially on forward bending of head, (c) periorbital puffiness, specially in morning, and (d) secondary anosmia/parosmia.

Examination may reveal: (a) sinus tenderness, (b) postnasal drip, and (c) inflamed nasal mucosa, and (d) co-existing otitis media.

Complications include: (a) recurrent respiratory infections, (b) orbital infections, e.g. cellulitis, abscess or osteomyelitis, (c) intracranial extension of infection, e.g. meningitis, sinus thromboses or subdural abscess.

Diagnosis is supported by presence of opacification, mucosal thickening or air-fluid levels on sinus X-rays

Fig. 16.5: Sinusitis.
Note mucosal edema and fluid collection in right maxillary sinus

with special views, e.g. *Water's or Caldwell's view* **(Fig. 16.5)**, which may be confirmed on CT scan. Etiological diagnosis needs examination of nasal fluid for eosinophils to exclude allergic etiology and sinus aspiration/culture, though rarely needed in immunocompetent children.

Management aims to: (a) control the infection by antibiotics, and (b) facilitate sinus-fluid drainage by decongestants, steam inhalation and positioning.

Oral amoxicillin with/without clavulanate is the drug of choice for acute sinusitis, though cephalosporins or levofloxacin (in older children) are equally effective. Treatment should continue for 14–21 days or at least 7 days after resolution of symptoms.

Chronic sinusitis for >12 weeks may be due to staphylococcal, anaerobic or fungal infections and must be treated with broad-spectrum antibiotics for 3–6 weeks, along with oral decongestants, nasal steroid sprays and saline irrigations, before considering surgical drainage of sinus.

16.5.3 THROAT DISORDERS

Throat is a common passage connected to nasal as well as oral cavity, consequently affected by variety of inhalant and ingestant insults. Three important protective lymphoid structures—two lateral tonsils and one adenoids on posterior nasopharyngeal wall, collectively form the *Waldeyer's ring*. Eustachian tube from middle ear also open into lateral wall of nasopharynx.

Acute tonsillopharyngitis (sore throat): While tonsillopharyngeal involvement is common in many respiratory or systemic illnesses, the term *acute tonsillopharyngitis* usually refers to primary inflammation of the throat.

Etiologically ~80% cases are caused by viral infections (RSV, influenza, entero or adenoviruses) and another

15–20% by Group A β hemolytic streptococci (βHS). Sore throat due to other causes, e.g. *Staph. aureus, S. pneumoniae* is rare and usually represents superinfection.

Epidemiology: Viral infections are perennial and more common in young children. Streptococcal sore throat (SST) is common in winter season and older children > 3 years.

Clinically, most cases present with acute onset of moderate fever, throat pain and dysphagia with constitutional features and a self-limiting course. Important clinical differences between viral and SST include:

- Presence of rhinitis, cough and hoarseness of voice is rare in SST and indicates viral etiology.
- Throat signs are generally minimal in viral illness while SST is associated with marked inflammation, follicular exudates and usually, tender cervical lymphadenopathy.

Centor criteria suggests score of 1 for each of the following five points: (a) absence of cough, (b) tender cervical lymphadenopathy, (c) fever >38°C, (d) tonsillar exudates/swelling and (e) age 3–14 years. Based on this score, risk of SST is stratified as low (1), moderate (2–3) and high (≥ 4).

Complications include: (a) *local extension* of infection, e.g. otitis media, retropharyngeal abscess and chronic tonsillitis, or (b) *systemic complications* of SST, e.g. rheumatic fever and acute nephritis.

Diagnosis is clinical though throat culture is indicated in—(a) suspected cases of SST with centor score >1, (b) past history of rheumatic fever/heart disease, (c) persistent signs for >3 days, and (d) suspected diphtheria. Antibody tests, e.g. ASO titres are usually negative in early SST.

D/D mainly includes diphtheria (tough membrane that bleeds on separation), infectious mononucleosis (atypical lymphocytes), early measles (Koplik spots > rash), etc.

Treatment: Viral sore throat is self-limiting and treated symptomatically with rest (including voice rest), warm saline gargles, soft-diet and antipyretics, e.g. Paracetamol.

Antibiotics are indicated only in culture-proven or high-risk cases of SST (Centor score 4), with oral penicillin (250–500 mg BD) or amoxicillin (50 mg/kg OD) for 10 days. Oral azithromycin (10–15 mg/kg OD × 3–5 days) or first-generation cephalosporins are equally effective and may be used, specially in Penicillin-allergic cases. *Cotrimoxazole, sometimes used for prophylaxis, should not be used for treatment of SST.*

Repeat throat cultures are not necessary after antibiotic therapy (except in rheumatic fever), as persistently positive cultures may be due to colonization/carrier state and need not be treated.

Prevention of SST is important, especially in cases with previous rheumatic fever, requiring long-term penicillin prophylaxis (Ch 17.6).

Chronic tonsillitis: Tonsils are normally enlarged in 4–8 years age-group due to normal lymphoid growth and all enlarged or hypertrophic tonsils should not be construed as chronic tonsillitis or indication for tonsillectomy.

Clinically, chronic tonsillitis is frequently associated with—(a) recurrent/persistent dry cough, (b) dysphagia, (c) growth failure, and (d) cervical lymphadenopathy.

Treatment: Most cases can be successfully treated with longer antibiotic therapy. *Tonsillectomy* is indicated only in—(a) chronic tonsillitis with severe airway obstruction and growth failure, (b) hypertrophied, non-inflamed tonsils persisting beyond 8–10 years of age and affecting growth, (c) peritonsillar abscess, and (d) to exclude tumors.

Tonsillectomy for recurrent tonsillitis is recommended only in cases with 7 documented episodes in the previous year *or* 5 episodes in each of the previous 2 years, or 3 episodes in each of the previous 3 years (*paradise criteria*).

Peritonsillar abscess (Quinsy) is the extension of pharyngotonsillitis into a potential space between superior constrictor muscle and tonsils, usually due to β *hemolytic streptococci* or *oral anaerobes*.

Clinically, apart from history of preceding sore throat, these cases present with high fever, severe throat pain, trismus (spasm of pterygoid muscles), dysphonia/slurred speech and torticollis. *On examination,* affected tonsillar area is marked by displacement of tonsils and/or pointing abscess over anterior faucial pillar, which may rupture spontaneously.

Treatment includes antibiotics and aspiration of pus with/without tonsillectomy.

Retropharyngeal abscess denotes extension of infection into the potential space between posterior pharyngeal wall and pre-vertebral fascia, as a complication of bacterial pharyngitis, vertebral osteomyelitis or penetrating injuries of pharynx.

Microbially, retropharyngeal abscesses are usually polymicrobial, with group A *streptococci*, *Staph. aureus* and *oral anaerobes* as predominant pathogens.

Clinically, these cases present with history of sore throat followed by high fever and severe dysphagia, dyspnea, throat pain. *On examination*, hyperextension of neck and a bulge in the posterior pharyngeal wall are strong indicators of retropharyngeal abscess.

Untreated cases may rupture into pharynx or extend within fascial plains to produce neck swelling or mediastinal mass. Death may ensue due to aspiration, airway obstruction or erosion of major vessels.

Diagnosis rests on lateral X-ray of neck suggestive of increased retropharyngeal space with soft tissue mass and must be confirmed by CT scan.

Fig. 16.6A and B: **Adenoids: (A) Adenoid facies; (B) Lateral X-ray showing obliteration of nasopharyngeal column.**

Treatment includes intensive therapy with a semi-synthetic penicillin, e.g. clindamycin *or* ampicillin + sulbactum, to cover penicillinase-producing staphylococci, along with surgical drainage of abscess.

Adenoidal hypertrophy is a common cause of chronic nasal obstruction, mouth-breathing and snoring in school children. Hypertrophy of nasopharyngeal adenoids may be developmental (normal lymphoid growth during 4–8 years) or post-infective, associated with faucial tonsillitis.

Clinically, these cases present with:

- *Persistent cough and rhinorrhea*, due to post-nasal drip.
- *Mouth-breathing* and *snoring* with disturbed sleep, due to airway obstruction.
- *Adenoid facies* with open mouth, high-arched palate and maxillary prominence **(Fig. 16.6A)**.
- *Complications*, e.g. (i) obstructive sleep apnea syndrome, (ii) failure to thrive due to chronic hypoxia, (iii) poor school performance due to disturbed night sleep, and (iv) chronic otitis media due to blocked eustachian tubes by hypertrophied tissue.

Diagnosis rests on lateral X-ray showing obliteration of nasopharyngeal air column **(Fig. 16.6B)**, indirect pharyngoscopy or fiberoptic nasopharyngoscopy.

Management: As developmentally hypertrophic adenoids often regress by 8–9 years, adenoidectomy is indicated only in—(a) persistent adenoids beyond >10 years, (b) recurrent nasopharyngitis or otitis media, (c) severe airway obstruction with growth failure or obstructive sleep apnea disorders.

Obstructive sleep apnea disorders (OSAD) is a common but under-diagnosed problem in childhood, characterized by—*a combination of prolonged partial airway obstruction and intermittent complete obstruction (obstructive apnea), which may disrupt sleep or cause more serious complications*, e.g. *growth failure, developmental delay and occasionally, sudden death*.

Incidence: OSAD is estimated to affect ~1% of school children, though *snoring*-the milder variant, is more common in 8–10%. OSAD is most common during 5–7 years of age due to physiological adenoidal hypertrophy, with equal sex distribution in children (in adults, more common in males).

Predisposing factors include—(a) adenotonsillar hypertrophy, (b) recurrent respiratory infections, (c) craniofacial abnormalities, e.g. cleft palate, micrognathia, macroglossia, etc. (d) neuromuscular or brain-stem disorders, (e) others, e.g. extreme obesity or sedative drug therapy.

Pathogenesis of OSAD involves a cyclic breathing irregularity due to failure in maintenance of normal airway tone during sleep. (sleep > decreased airway tone > airway narrowing > OSAD > hypoxia/hypercapnia > increased ventilatory efforts > arousal > increased airway tone > relieved airway obstruction > return to sleep).

Clinical spectrum varies from habitual snoring to severe sleep disturbances and consequences of prolonged hypoxia. Important problems include:

- *Airway obstruction*: Snoring, mouth-breathing, adenoid facies, pectus excavatum, stridor, etc.
- *Disturbed sleep*: Daytime sleepiness, behavioral problems, poor school performance.
- *Chronic hypoxia*: Growth failure, polycythemia and hemodynamic changes, e.g. pulmonary hypertension and right ventricular hypertrophy in severe cases.

Diagnosis rests on a *clinical triad* of—(a) snoring, (b) nocturnal breathing difficulties, (c) witnessed breathing pauses; which may confirmed on *polysomnography* in borderline cases.

Other findings, e.g. large adenoids, respiratory alkalosis with metabolic acidosis and unexplained polycythemia supports the diagnosis.

D/D of OSAD includes other causes of disturbed night sleep like nocturnal asthma, gastroesophageal reflux and behavioral problems, e.g. night terrors and narcolepsy.

Treatment: As adenoidal hypertrophy is the commonest cause, adenotonsillectomy is the first step in treatment of significant OSAD. Non-responders may need night-time breathing support, e.g. CPAP to keep their airways open.

Pharmacotherapy is of limited value in children, while Medroxyprogesterone acetate (to stimulate ventilatory drive) and Protriptyline (to decrease REM sleep) have been found effective in adults. Extreme cases may require permanent tracheostomy or facial reconstructive surgery.

Pharyngeal foreign bodies, e.g. fish-bones, present with dysphagia or prickly sensation in throat. Visible foreign bodies can be removed by *Tongue-jaw lift maneuver* (Ch 27.1.1), but blind finger-sweeps should never be attempted, which may push the body further back into airways or esophagus.

A neck and chest skiagram is advised in all cases to exclude deeper (airway/esophageal) foreign bodies or left-outs after removal.

16.5.4 EAR DISORDERS

External and middle ear as well as ossicles develop from first two branchial arches and grooves, while rest of the inner ear develops from otocyst.

Congenital malformations of ear include: (a) external ear abnormalities, e.g. preauricular pits/tags or microtia, (b) external auditory canal atresia/stenosis, (c) ossicular malformations, leading to conductive deafness and (d) congenital perilymphatic fistula, leading to sensorineural deafness.

Malformations of external or middle ear, though largely benign and cosmetic, are frequently associated with inner ear defects or other congenital anomalies, e.g. renal malformations or chromosomal syndromes. Hence, complete auditory and renal evaluation is necessary in all children with ear malformations, along with cosmetic or functional interventions.

Otitis externa: While external ear canal is colonized by various aerobic and anaerobic organisms, it is protected by presence of a water-repellent waxy *cerumen*, derived from apocrinal and sebaceous secretions and exfoliated skin.

Otitis externa is the acute or chronic inflammation of external ear canal, sometimes associated with furunculosis or eczematous lesions.

Etiology: Excessive wetness, (e.g. swimming), dryness (lack of cerumen), trauma (foreign body) or neighbouring skin infections are predisposing factors for otitis externa, usually caused by *Pseudomonas, Staph. aureus*, anaerobes and occasionally, Candida (Otomycosis).

Clinically, these cases present with—(a) acute otalgia that typically accentuates on pressing the tragus or moving the pinna, (b) edema, redness and thick, clumpy otorrhea in ear canal, with or without, (c) temporary conductive hearing loss. Itching is more prominent in chronic otitis externa or otomycosis, while furunculosis is an extremely painful superficial abscess.

Diagnosis rests on otoscopic examination to rule out foreign body or furunculosis. Presence of herpetic vesicles on external auditory canal and pinna along with facial paralysis is termed *Ramsay-Hunt syndrome.*

Management includes—(a) topical antibiotics and/or antifungal drops, (b) oral analgesics, and (c) local anesthetic ear drops in severe painful ear. During early stages, when edema may prevent entry of topical drugs in ear canal, a cotton-wick soaked with desired topical drug may be used to facilitate drug delivery. Ear should be thoroughly cleaned with irrigation after control of acute inflammation to prevent recurrence.

Otitis media (OM), i.e. inflammation of middle ear cleft, includes a spectrum of ear-pathology, classified in order of increasing severity as: *(a) acute otitis media without effusion, (b) acute otitis media with effusion, (c) chronic otitis media with effusion (OME), and (d) chronic suppurative otitis media (CSOM) with/without cholesteatoma.*

Epidemiology: Nearly 2/3rd of children have at least one attack of OM by 3 years of age, with highest incidence in late infancy (6–12 months). It is more common in boys and during winter season.

Important risk factors of OM include: (i) top feeding, (ii) foreign body, (iii) passive smoking, (iv) recent measles, (v) gastroesophageal reflux, (vi) immunodeficiency disorders, and (vii) institutionalized care in orphanages, etc.

Pathogenesis: OM is more common in younger children due to: (a) relatively horizontal position of eustachian tube, preventing adequate drainage, and (b) higher incidence of nasopharyngeal infections and adenoidal hypertrophy, which block the opening of eustachian tube due to mucosal edema. Gradual absorption of air in middle ear after eustachian tube obstruction results in negative pressure > transudative effusion > secondary infection > rise in middle ear pressure > perforation of tympanic membrane.

Microbial etiology: *Strept. pneumoniae* (30–50%) and *H. influenzae* (20–30%) are two commonest pathogens in OM, followed by others, e.g. *S. aureus, Moraxella catarrhalis, E. coli,* Klebsiella and Pseudomonas. OM due to mycoplasma, chlamydia, tuberculosis, viruses and anaerobic organisms is relatively rare.

Clinically, acute OM presents with sudden onset of severe otalgia, otorrhoea, fever and constitutional symptoms, usually during or soon after common cold. GIT upsets is common in young infants.

Direct visualization of tympanic membrane reveals congested, opaque, bulging tympanic membrane with restricted mobility, with/without perforation and suppurative discharge. Foreign bodies should also be excluded on otoscopy.

CSOM presents with persistent ear discharge for > 6 weeks with non-intact tympanic membrane, broadly categorized as-(a) *Safe* with simple central perforation of parse tensa or (b) *Unsafe* perforations involving attic and posterosuperior region with high-risk of intracranial complications and cholesteatoma

Complications include: (a) hearing loss, (b) infection of surrounding structures, e.g. labrynthitis, mastoiditis or petrositis, (c) intracranial infections, (d) tetanus, (e) cholesteatoma, and (f) facial palsy.

Diagnosis is based on otoscopy, supported by ear-swab cultures. Although tympanocentesis for fluid culture is more reliable for microbial diagnosis, it is indicated only in cases with: (a) poor therapeutic response, (b) serious or immunodeficiency illness, (c) co-existing intracranial infection.

For common causes of otalgia *see* **Table 16.15**.

TABLE 16.15: Common cause of otalgia (earache)

- Otitis media (or blocked Eustachian tubes)
- Otitis externa, i.e. furunculosis, herpes, otomycosis
- Foreign body or trauma
- Impacted cerumen (wax)
- Referred pain from teeth, temporomandibular joint, etc.

Treatment: *Antibiotic therapy* in OM is largely empirical, based on local drug sensitivity profile. Oral amoxicillin (40–50 mg/kg/d q8hr) for 10 days is the drug of choice in most cases. Higher doses (75–90 mg/kg/day) must be considered in populations with higher risk of resistance. Other drugs like Coamoxiclav or second-generation cephalosporins may be used in resistant cases.

Supportive therapy includes analgesics, decongestants, e.g. pseudoephedrine, and local hot fomentation. Antihistamines and steroids are not useful.

Surgical interventions, e.g. myringotomy with Tympanostomy tube placement may be needed in cases with severe AOM, CSOM or recurrent OM. These tubes usually extrude spontaneously in 6–9 months.

Recurrent OM, defined as > 2 episodes in 6 months or >3 episodes in a year, should be considered for tympanostomy tube insertion and adenoidectomy to reduce the frequency of episodes.

Mastoiditis, i.e. *inflammation of mastoid air cells*, is an important complication of otitis media.

Clinically, it is characterized by retroauricular pain/tenderness, induration, redness and downward/outward shifting of pinna with blurring of postauricular sulcus and sometimes, formation of mastoid abscess. Infection may extend intracranially to cause meningitis or brain abscess *or* rupture externally.

Diagnosis rests on clinical features and lateral X-ray of the skull, revealing: (a) haziness of mastoid outline, (b) loss of pneumatization, and (c) sclerosis of air-cells in chronic mastoiditis. CT scan is necessary to confirm the diagnosis and exclude intracranial extension.

Treatment depends on the severity of disease, including antibiotics (as for AOM), drainage of pus (if localized) and mastoidectomy in extensive or chronic disease.

Foreign body in ears, e.g. insects, left-over cotton buds and grains, etc., are common in all age-groups and usually present after many days with earache, discharge, tragus swelling, ringing sensation or temporary deafness. Tympanic perforation and tetanus are most important complications.

Visible foreign bodies may be removed by a sterile, wet cotton-bud or forcep, followed by instillation of topical antibiotic drops. However, long-standing bodies may be impacted or tend to move further inside on repeated attempts and need auroscopic or surgical removal by otolaryngologists.

Also see IMNCI guidelines for management of child with ear problems (Ch 29).

16.6 ACUTE CROUP

Croup is a clinical term to describe *'a heterogeneous group of upper airway disorders, all characterized by typical brassy or metallic cough with or without stridor, hoarseness and respiratory distress, due to variable degree of airway obstruction'*.

TABLE 16.16: Common causes of acute croup

Bacterial
- Acute epiglottitis *(H. influenzae)*
- Bacterial tracheitis *(Staph. aureus)*
- Diphtheria

Viral *(Parainfluenza)*
- Acute laryngotracheobronchitis
- Acute infectious laryngitis

Allergic *(?)*
- Acute spasmodic laryngitis

Most of these cases are viral in origin, with diphtheria becoming a rarity in vaccination era. Common causes of croup may be classified according to site of lesion or according to the etiology **(Table 16.16)**.

Acute epiglottitis (AE) is an uncommon but life-threatening cause of croup, caused by *H. influenzae type b (Hib) infection.*

Clinically, AE is rare in infancy, with maximum incidence in 2–5 years age group.

Typically, these cases are apparently well at bedtime but wake up in night with—(a) high fever and sore throat, (b) rapidly progressive respiratory distress with stridor and drooling, (c) brassy cough, i.e. croup, dysphonia and dysphagia, (d) *hyperextension of neck*-a protective action to keep the airway open, and (e) cyanosis, agitation or impaired sensorium.

Throat examination reveals a *swollen cherry-red epiglottis,* though it should be deferred till resuscitation facilities are available as use of tongue depressor may lead to sudden laryngospasm.

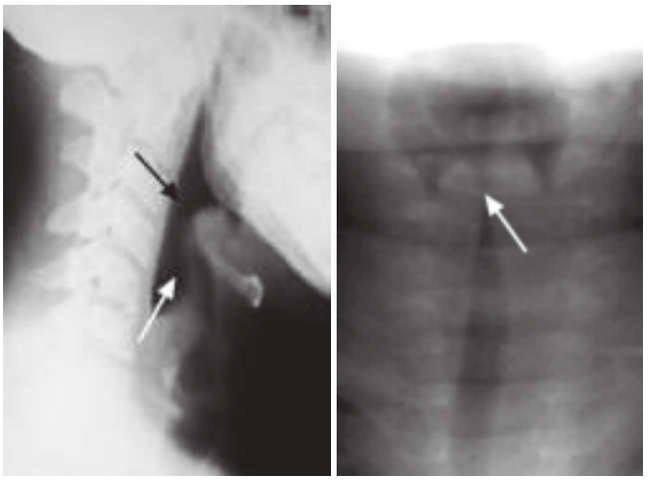
Diagnosis depends on-(a) throat examination, (b) X-ray neck showing *Thumb sign* on lateral view and *Steeple sign on AP view* **(Fig. 16.7)**, and (c) laryngoscopy in doubtful cases.

Treatment: Epiglottitis is an emergency, which requires—(a) immediate hospitalization, (b) airway maintenance with endotracheal intubation or tracheostomy, (c) fluid and electrolyte correction, and (d) antibiotics. Anxiety-provoking interventions such as phlebotomy, venous cannulation or throat examination should be avoided until the airway is secure.

IV Ceftriaxone 50 mg/kg/d q8–12hr (or cefotaxime) for 7–10 days, is the drug of choice due to rising incidence of ampicillin-resistant HiB infections. Nebulizations, steroids and racemic epinephrine are of no proven value.

Most cases recover within 2–3 days of therapy, though mortality is high (5–10%) in untreated cases.

Acute laryngotracheobronchitis (ALTB) is the commonest cause of croup in childhood, usually due to



Thumb sign (lateral view) Steeple sign (AP view)

Fig. 16.7: **Acute epiglottitis (neck X-rays).**

parainfluenza viruses (75%), and less frequently by other viruses, e.g. adenovirus, RSV, etc. Secondary bacterial infection is rare.

Clinically, ALTB presents in 1–3 years age group, with a characteristic sequence of events:

- Mild upper respiratory illness with brassy cough for 1–2 days, followed by
- Progressive stridor, croup and respiratory distress, which typically worsens at night, partly relieves in day and then recurs again on subsequent nights,
- Gradually recovery in 3–7 days with residual cough.

On examination, high fever is rare and throat is usually normal. Air entry may be reduced in acute phase with few rhonchi or crepitations. Signs of hypoxia, e.g. cyanosis or altered sensorium may develop in severe cases.

Complications are uncommon (<15%) and include direct extension of infection, e.g. otitis media, bacterial tracheitis and bronchopneumonia. Recurrences till 5–6 years of age are common.

Diagnosis is clinical, though lateral X-ray of the neck may show *Steeple sign—narrowing of tracheal air column below the glottic area.* Careful throat examination for absence of cherry-red epiglottis and thumb sign on neck X-ray excludes epiglottitis.

Treatment includes:

- Humidified oxygen to maintain SpO_2 >95%;
- Racemic epinephrine (1:1000) nebulisation as 0.5 ml/kg, mixed with normal saline to make total volume of 5 ml (maximum dose 5 ml of undiluted solution). Second dose may be repeated after 2 hours, if required.
- Steroids, either as single dose of PO/IV *dexamethasone* (0.6 mg/kg) or nebulized *budesonide* (1 mg) twice a day for 2 days.
- Correction of fluid/electrolyte imbalance, and
- Constant monitoring.

Benefits of multiple doses of steroids are uncertain. Endotracheal intubation or tracheostomy may be needed in severe cases. Antibiotics have no role in ALTB *per se*, though may be given if epiglottitis can't be excluded. Sedatives are contraindicated and may mask signs of impending respiratory failure.

Acute infectious laryngitis is the more localized variant of ALTB with similar etiology and milder clinical presentation, limited to hoarseness or loss of voice without respiratory distress.

Acute spasmodic laryngitis also has similar clinical presentation with following differences:

- Absence of fever or other features of infection,
- Family history of similar episodes in some cases,
- Shorter duration of episodes

Exact cause is unknown, probably related to GER, atopy or emotional disturbances.

Bacterial tracheitis is more likely a serious complication of ALTB rather than a separate disease, due to superadded *Staph. aureus* infection.

Clinically, most cases are <3 years old and present after few days of ALTB attack with—high fever, toxic appearance, brassy cough and thick purulent secretions on endotracheal suction.

Diagnosis: Chest X-rays may show subglottic airway narrowing with ragged tracheal air-column (irregular tracheal walls) and patchy lung infiltrates.

Treatment: Apart from supportive measures, specific anti-staphylococcal therapy with *cloxacillin* or *vancomycin* is essential.

Foreign bodies (FB) are important cause of croup, stridor and sometimes accidental deaths in pre-school children, once lodged in supraglottic region or deeper airways, e.g. trachea or bronchi.

Laryngeal FB present with sudden choking, dyspnea, stridor or croup. *Whistle sign*—a typical whistling sound on inspiration and expiration may be present in laryngeal obstruction due to toy whistles.

Considering immediate risk of death, first-aid measures, e.g. *back-blows and chest thrust maneuver* in infants and *Heimlich maneuver* in older children may be attempted, provided: (a) FB is witnessed or strongly suspected, (b) expert help is not immediately available. (Ch 27.1.1). However, since these procedures carry a risk of converting partial obstruction to complete airway block, it is essential to obtain expert help as early as possible.

Diagnosis may be confirmed on lateral neck X-ray (d/d esophageal FB), or direct laryngoscopy, which is also required from removal. Pre-procedure tracheostomy is advisable in dyspneic children.

Bronchial FB may be asymptomatic or presents with signs of airway irritation, e.g. cough, dyspnea, blood-streaked sputum or recurrent respiratory infections.

These FB are more common on right side due to straighter right bronchus.

Clinicoradiological signs depend on the extent of obstruction with two distinct pathologies—(a) partial *ball-valve* obstruction, leading to distal emphysema, and (b) complete obstruction with distal collapse.

Bronchoscopic removal is the treatment of choice, preferably with a rigid bronchoscope due to wider lumen and separate oxygen channel.

Chest X-ray is essential in all these cases to determine the extent of pulmonary pathology, even after FB removal. While most collapse/emphysema improve after FB removal, persistent lesions may require lobectomy, due to risk of recurrent infections and bronchiectasis.

Laryngomalacia is the commonest congenital abnormality of larynx, characterized by *developmental floppiness* of arytenoid cartilages, epiglottis or aryepiglottic folds, leading to inspiratory airway obstruction. About 1/3rd of these cases also have tracheomalacia or bronchomalacia.

Clinically it presents in neonatal period with *inspiratory stridor of variable intensity that worsens in supine position and relieved in prone position*, with/without hoarse cry. Respiratory distress is rarely severe, though some cases with prolonged or severe obstruction may develop thoracic deformity and growth failure. Presence of co-existing GERD enhances the severity of manifestations.

Diagnosis is clinical, based on postural changes in intensity of stridor *and* disproportionately less respiratory distress. Direct laryngoscopy may be needed to exclude other causes of stridor (Ch 16.4.3) in early infancy.

Treatment: No specific therapy is indicated, as most children outgrow it by 3–6 months of age, after growth and maturity of airways. Nursing in the prone position and slow careful feeding is enough for most cases. Endotracheal intubation or tracheostomy is rarely required.

Surgical intervention, e.g. *supraglottoplasty* should be considered only in very severe and persistent cases. Proton pump inhibitors may be useful in cases with associated GERD or laryngopharyngeal reflux disease.

16.7 ACUTE BRONCHIOLITIS

Acute bronchiolitis is a common viral illness in infancy, characterized by *acute, self-limiting inflammation and obstruction of smaller airways.*

Etiology: *Respiratory syncytial virus* (RSV) is the commonest cause of bronchiolitis in >50% cases. Other causes include *parainfluenza type 3, mycoplasma, and adenoviruses.*

Epidemiology: Acute bronchiolitis is almost exclusively seen during first two years of life, most commonly from 3–6 months of age. Maximum cases occur in winter or early spring season. Male sex, top-feeding, overcrowding and passive smoking are other high-risk factors.

Etiopathogenesis: Infection is usually acquired from a family adult or older child, suffering from minor viral illness. Viral invasion leads to mucosal edema and collection of mucus and cellular debris in smaller bronchioles with consequent airway obstruction. As airway diameter is comparatively smaller during expiration, obstruction is predominantly expiratory and leads to distal air trapping with patchy emphysematous and atelectatic areas (after absorption of trapped air). Diminished ventilation produces hypoxemia, hypercarbia and respiratory acidosis.

Clinically, these cases present with:

- Preceding history of mild viral illness for 2–3 days, followed by:
- Acute onset of moderate fever with *wheezy* cough and feeding difficulties, and
- Rapidly progressive respiratory distress with over-inflated chest (due to air trapping), diminished air entry and few rhonchi and fine crepitations. *Auscultatory finding in bronchiolitis are disproportionately less than the severity of distress*.
- Self-limiting course with gradual recovery in 2–3 days. Less than 1% cases progress to respiratory failure.

Diagnosis depends on: (a) clinical grounds, i.e. *age* and *paucity of lung signs despite severe dyspnea,* and (b) chest X-ray showing *diffuse hyperinflation of lungs* with pushed down diaphragm and patchy areas of atelectasis or consolidation **(Fig. 16.8)**.

Although rarely possible, virus may be demonstrated in nasopharyngeal secretions by ELISA, PCR or culture.

D/D: Bacterial pneumonia and asthma are two important D/Ds for acute bronchiolitis.

Presence of high fever, significant auscultatory and radiological findings and polymorphonuclear leukocytosis indicates bacterial pneumonia.

Fig. 16.8: Acute bronchiolitis: Bilateral hyperinflated lung fields on X-ray chest.

TABLE 16.17: D/D acute bronchiolitis and asthma

Feature	*Bronchiolitis*	*B. asthma*
Common age	<1 year	>1 year
Past history	None	Recurrent
Family history	Absent	Present
Prodromal URTI	+	+
Fever	+	+
Lung signs	Minimal	Ronchi ++
Eosinophilia	–	+
Response to Rx*	Poor	Good

*to Nebulized salbutamol

Initial attacks of asthma and bronchiolitis are almost indistinguishable though following features suggest possibility of asthma: (a) family history of atopy, (b) recurrent attacks, (c) eosinophilia, (d) absence of fever and (e) response to nebulized salbutamol **(Table 16.17)**.

In general, first episode of wheeze following an upper respiratory tract infection in children less than 2 years of age is presumed to be bronchiolitis.

Management: Hospitalization is indicated in cases with (a) respiratory rate >60/minute, (b) severe chest indrawing, (c) presence of danger signs (inability to feed, vomiting, seizures or altered sensorium), (d) SpO_2 <92% or (e) those staying away from hospitals. Treatment is largely supportive with:

- Humidified oxygen with regular oxygen saturation (SpO_2) monitoring. Severe cases may require CPAP, assisted ventilation or even extracorporeal membrane oxygenation.
- Nursing in semi-sitting position with head and chest elevated at 30° and neck extended.
- Fluid and electrolyte correction, with additional fluids for insensible water loss.
- Nebulizations with hypertonic saline, salbutamol or adrenaline are of no consistent benefit but may be continued every 4–6 hours in cases, who respond to the first dose.
- Antibiotics, no value for viral disease, are commonly used to prevent superadded bacterial infection.
- Steroids, antihistamines, nasal decongestants, chest physiotherapy, steam inhalation etc. should be strictly avoided. Nose block may be cleared with saline nasal drops and gentle suctioning. Sedatives are contraindicated and may mask signs of respiratory failure.
- *Ribavarin*-a specific antiviral agent (given as aerosol), though not useful routinely, may be used in cases with pre-existing lung or heart disease or immunodeficiency.

Prevention: RSV-specific immunoglobulin or monoclonal antibodies (*Palivizumab*) may be given prior to RSV season in high-risk cases, e.g. those with chronic lung disease. However, *hand hygiene* is the best measure to prevent transmission of viruses responsible for bronchiolitis.

Acute bronchitis usually follows a viral upper respiratory tract infection, leading to protracted cough due to inflammation and hypersensitization of airways. Initial dry, hacking cough of acute illness may become productive after several days with purulent sputum. Chest pain and vomiting during or after a bout of cough are common. Mucus gradually thins and cough abates over next 2–3 weeks.

Chest examination and radiographs are usually normal, unlike in pneumonia. Treatment is nonspecific with no role of antibiotics. Cough syrups and antihistamines may provide temporary relief but dry-up the secretions and can mask serious disease, hence, not recommended.

Chronic bronchitis with productive cough of >3 months each year for >2 years, is not as well-defined entity in children as in adults. Rather than the environmental factors, it may be an indicator of serious underlying illness and must be investigated.

Bronchiolitis obliterans: Bronchiolitis obliterans is a chronic lung disease with progressive airway obstruction by nodular masses of granulation and fibrosis, presumably due to exaggerated reparative response after viral infections *or* exposure to drugs, e.g. penicillamine or chemical inhalants, etc.

These cases present with gradually progressive dyspnea, cough with expectoration and wheezing. Chest skiagram may reveal miliary mottling or unilateral hyperlucency (*Swyer-James syndrome*). Lung biopsy is diagnostic. There is no specific treatment, though prolonged steroid therapy may retard the progression of disease.

16.8 BRONCHIAL ASTHMA

Bronchial asthma, the commonest chronic respiratory disease in childhood, is characterized by recurrent paroxysmal wheeze, dyspnea and cough; due to reversible and dynamic narrowing of airways associated with bronchial hyperreactivity.

Global initiative against asthma (GINA) guidelines 2023 define asthma as "*a heterogeneous disease, usually characterized by chronic airway inflammation with history of respiratory symptoms, e.g. wheeze, cough, breathlessness and chest tightness, which vary over time and intensity, together with variable expiratory airflow limitation.*"

Incidence of asthma in Indian school children is estimated to be ~10–15% and seems to be rising. In addition, a larger population demonstrates bronchial hyperreactivity on exercise (exercise-induced asthma) or at potential risk for asthma due to family history of atopy.

Etiopathogenesis of asthma is complex, involving three major components: (a) *hyperreactivity of airways, (b) allergen-induced sensitization, and (c) triggering factors*.

a. Hyperreactivity of airways may be genetically determined (inherent) *or* acquired after non-specific inflammation of these airways due to preceding viral infections.

Maintenance of airway diameter is a function of balance between bonchodilatory *adrenergic* and Bronchoconstrictory *cholineregic* activity. Airway hyperreactivity indicates either—(a) impaired β-adrenergic activity due to abnormal adenylate cyclase function, and/or (b) increased cholenergic activity due to lower threshold of cholinergic receptors.

Role of inherent hyperreactivity is supported by following facts: (a) family history of atopy is present in ~50% cases, (b) a child with one affected parent has ~25% risk of developing asthma, while it rises to ~50%, if both parents are affected, and (c) bronchial lability on exercise-testing has been demonstrated in otherwise healthy relatives of asthmatic children.

b. Atopy, i.e. *IgE mediated hypersensitivity* to external allergens is perhaps the most important cause of airway obstruction during acute asthmatic exacerbations. Common allergens include:

- *Inhalant allergens*, e.g. pollens, dust and mites, danders (suspended allergens from household pets or insects), fungi, etc., and
- *Ingested allergens*, e.g. food allergy, though frequently implicated in asthma, true relationship between *in vitro* reactivity to food items on skin testing and actual *in vivo* precipitation of bronchospasm is rarely strong.

To recapitulate, important events in IgE mediated hypersensitivity reactions (Ch 8.4.1) include:

- ***Sensitization*** to an allergen during initial exposure, with formation of specific IgE antibodies, which attach themselves to the surface of mast cells and basophils;
- ***Re-exposure*** to the same allergen, leading to antigen-antibody interaction on the surface of sensitized mast cells > degranulation > release of chemical mediators. Consequently, two types of reactions are seen-
  - *Early phase reactions* (within 20 minutes) due to release of pre-formed mediators, e.g. histamine and eosinophil-chemotactic factors (ECF), etc., presenting with acute bronchospasm and preventable by mast-cell stabilizing agents, e.g. cromolyn sodium.
  - *Late-phase reactions* (after 4–12 hours), due to influx of inflammatory cells at the site of exposure and release of other chemical mediators, e.g. leukotrienes and prostaglandins. These mediators amplify allergic inflammation (reappearance of symptoms), facilitate further IgE production (accentuated hyperreactivity on repeated attacks) and produce more persistent airway obstruction (chronic disease). Late-phase reactions do not respond well to bronchodilators, but may be reduced by steroids.
- ***Trigger factors:*** Many non-immunological trigger agents are known to precipitate or aggravate the attacks in asthmatic children with or without atopy. A preceding mild viral infection is the commonest trigger for asthma in children, while others include-air pollutants, (e.g. smoke), exercise, weather changes, emotional disturbances, drugs, (e.g. aspirin) and endocrinal disturbances (as seen during premenstrual period). These factors probably act by inducing non-specific inflammatory reaction on exposure.

Exercise is known to trigger asthma in susceptible children due to loss of water and heat from airways, leading to mucosal hyperosmolarity and release of inflammatory mediators from mast cells. Similar reason is proposed for asthma triggered by weather changes, i.e. dryness of airways along with changes in airborne allergens.

Pathophysiology: Bronchial asthma is present considered as primarily a *chronic inflammatory disease*, predominantly involving medium and smaller airways with:

- *Persistent partial airway obstruction due to mucosal inflammation and increased mucus production, leading to* air trapping in distal air passages;
- *Paroxysmal, dynamic and reversible obstruction due to bronchospasm, temporarily aggravating pre-existing airway obstruction*
- *Airway obstruction due to above reasons, leading to* air trapping in distal air passages. Obstruction is more severe during expiration due to rise in intrathoracic pressure and may lead to distal hyperinflation/emphysema (partial obstruction/ball-valve mechanism) or atelectasis (complete obstruction).
- *Mismatched ventilation-perfusion* in different parts of lung with alveolar hypoventilation, leading to progressive hypoxia, hypercapnia and acidosis; culminating to respiratory failure in severe/untreated attacks **(Fig. 16.9)**.

Clinical manifestations of asthma are interspersed with paroxysmal exacerbations and depend on the severity of bronchoconstriction during attacks as well as in inter-attack period. Important attributes of these attacks are:

- *Age of onset:* Nearly 80% of asthmatics manifest by 5 years. Asthma is more severe in younger children, due to smaller airways size. However, only minority of them continue to have persistent asthma in late childhood.
- *Seasonal variation:* Acute attacks are more frequent in spring or rainy season, though many children have perennial disease.
- *Diurnal variations:* Most acute attacks begin during night or early morning, when the normal airway diameter is lowest in 24 hours.

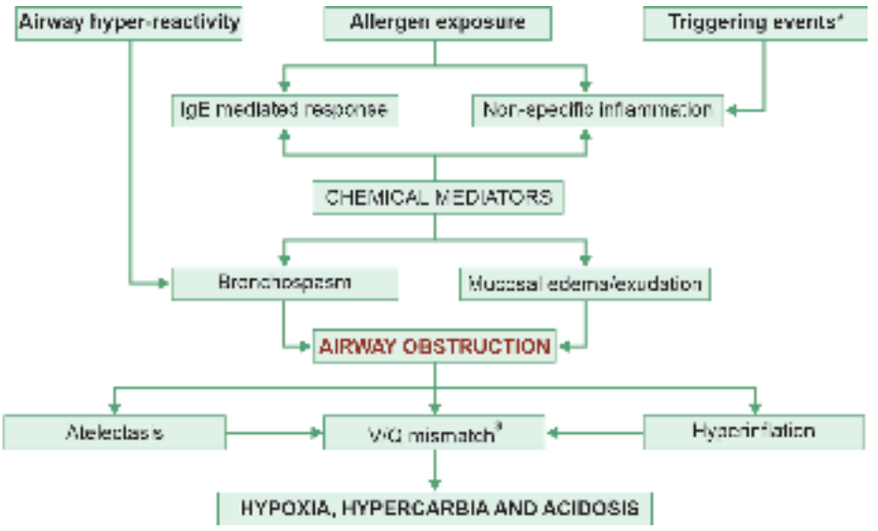


Fig. 16.9: Pathophysiology of asthma.

*Triggering events, e.g. viral infection, exercise, emotional disturbances, air pollutants.
$Ventilation: perfusion mismatch, leading to alveolar hypoventilation.

- *Preceding events:* Although triggered by many factors, a mild viral respiratory infection is the commonest preceding event for acute attacks.

Acute asthmatic exacerbation may be paroxysmal or gradual in onset and presents with—(a) non-productive cough, (b) wheezing, and (c) dyspnea. Other symptoms, e.g. abdominal pain or vomiting due to strenuous diaphragmatic contractions, or altered sensorium due to cerebral hypoxia is common in severe attacks.

Examination reveals—(a) hyperinflation of chest, (b) diminished air entry, and (c) presence of rhonchi all over the lungs. Severe cases may also develop, (d) cyanosis, and (e) pulsus paradoxus.

Status asthmaticus denotes an *acute exacerbation, refractory to usual therapy and with potential risk for respiratory failure*. Development of drowsiness or confusion, bradycardia, and disappearance of wheeze and pulsus paradoxus despite progressive dyspnea, indicates imminent respiratory failure.

In between the attacks, child may be asymptomatic or has evidence of chronic airway obstruction, e.g. (a) barrel shaped chest, (b) persistent irritating cough, (c) poor exercise tolerance, and (d) growth failure.

Clinical asthma variants: Many children with hyper-reactive airways present with more non-specific manifestations, termed as *asthma variants*, rather than classic paroxysmal attacks. Common asthma variants include-*chronic noctural cough*, *infection-associated wheeze*, *exercise intolerance* (exercise-induced asthma), *postural asthma* (related to gastroesophageal reflux), Obesity-associated asthma, etc.

Diagnosis of asthma depends on:

- *Clinical presentation:*
  - *Combination of wheeze, dyspnea and cough,*
  - Recurrent and paroxysmal nature of attacks,
  - History of triggers, e.g. preceding viral infection,
  - Family history of atopic disorders in most cases.
- *Pulmonary function tests* suggestive of:
  - *Obstructive airway disease* (*low* FEV_1 or PEFR, usually <80%),
  - *Reversibility,* i.e. >12% rise in FEV_1 or PEFR after salbutamol nebulisation,
  - *Diurnal variability,* i.e. average >13% difference in morning vs evening PEFR over two weeks,
- *Laboratory evaluation* to identify:
  - Allergic etiology-eosinophilia and IgE levels,
  - Specific allergens by*:
    - *In vivo* skin or bronchial challenge tests,
    - *In vitro* RAST test for specific IgE antibodies,
  - *Co-pathologies:* Chest X-ray, mantoux test, etc.
  - Severity of the attack by blood gas analysis.

**See* Ch 8.4.1 for details. Bronchial challenge tests are risky and rarely used in practice.

Peak expiratory flow rate (PEFR), defined as the *measure of greatest flow rate on forced expiration after complete inspiration,* is a simple and reliable indicator of the degree of airway obstruction in asthma. It may be easily measured in cooperative school-age children by *Mini-Wright* peak flow meter, recording the *best* of three efforts (Ch 32.5).

PEFR is widely used in clinical practice to:

- *Monitor the course of disease* using ***personal-best PEFR***, i.e. highest PEFR record in absence of acute attack, as an individual benchmark. Personal best PEFR changes with therapy and should be revised frequently.
- *Assess the severity of acute attack,* by percentage change from personal-best PEFR, as mild (PEFR >80%), moderate (50–80%) and severe (<50%).

- *Evaluate the therapeutic response* during acute attack.
- PEFR should *not be used to confirm the diagnosis of asthma*, though-(a) PEFR < 80% for height during attack, and (b) >15–20% rise over basal values after salbutamol nebulisation, suggest a strong possibility.

D/D of asthma includes other causes of recurrent wheeze (Ch 16.4.4) specially—(a) *acute bronchiolitis* **(Table 16.17)**, (b) infection-associated wheeze in *pneumonia* (d/d X-ray chest), and (c) *tropical pulmonary eosinophilia* (d/d AEC >2000, response to Diethylcarbamazine).

Conventionally, childhood wheezers have been classified on the basis of: (a) triggers, i.e. episodic whizzers or multi-triggered wheezers, or (b) time-trends of onset and course of symptoms, as follows:

- *Early-onset transient wheezers*, who begin wheezing in infancy, often triggered by viral respiratory infections and usually overgrow wheeze by 3 years of age.
- *Late-onset intermittent wheezers*, who present from 1–3 years of age and may continue wheezing till 5–6 years, before improvement.
- *Late-onset persistent wheezers*, who start wheezing after 3 years and generally continue to suffer till adolescence. Family history of atopy is common in them.

Late-onset persistent wheezers usually represent typical phenotype of asthma, while early-onset transient wheezing is usually due to non-asthmatic causes. However, clinical usefulness of such phenotype classifications is uncertain in predicting the risk of asthma.

Management of asthma aims to (a) control the acute attacks and their complications, and (b) improve quality of life with long-term control.

For simplicity, it has been discussed into following sections—(a) anti-asthmatic drugs, (b) management of acute attacks, and (c) long-term control of asthma.

I. Anti-asthmatic Medications

Anti-asthma drugs are broadly classified as: (a) *Relievers* for quick relief of symptoms, e.g. rapid-acting bronchodilators, (b) *Maintenance drugs* for use every day even in absence of symptoms (previously termed as controllers) including inhaled corticosteroids (ICS) and long-acting bronchodilators, and (c) *Anti-inflammatory relievers* (AIR), which contain combinations of both a low-dose ICS and a rapid-acting bronchodilator. Some commonly used drugs in bronchial asthma are as follows **(Table 16.18)**.

- ***β-agonists*** act by increasing β-adrenergic activity via adenylate cyclase activation and include *short-acting* (SABA), e.g. salbutamol or terbutaline, and *long-acting* (LABA), e.g. salmeterol or formometerol. SABA are preferred as *relievers* for acute exacerbations while LABA are used for maintenance in children >4 years. *LABA should never be used alone*, always as inhalers in combination with ICS. Non-selective adrenergics, e.g. adrenaline or isoprenaline are rarely used due to cardiovascular side effects.
- ***Anticholinergic agents,*** e.g. ipratropium bromide, inhibit vagus-mediated bronchoconstriction and potentiate bronchodilatory action of β-agonists, mainly used as second-line *reliever* in refractory acute attacks. Another anticholinergic-*Tiotropium bromide* inhaler, may be used for maintenance in severe uncontrolled asthma above the age of 6 years.
- ***Corticosteroids,*** as potent anti-inflammatory agents, are cornerstone of maintenance therapy in asthma, generally used in inhaled form (ICS) including short-acting beclomethasone or long-acting budesonide or fluticasone. However, systemic steroids, e.g. hydrocortisone or prednisolone are also used as *rescue therapy* in severe acute exacerbations to minimize the need for hospitalization and suppress late reactions.
- ***Leukotriene inhibitors*** *(LTRA)*, e.g. montelukast or zafirlukast antagonize late-phase reactions and thus have synergistic effect with steroids. These drugs are used either alone or along with steroids in—(a) long-term management of mild/moderate persistent asthma, or (b) prevention of exercise-induced asthma.
- ***Xanthine derivatives,*** e.g. aminophylline (85% theophylline) inhibit phosphodiesterase – a cyclic AMP degrader enzyme to raise cyclic AMP activity and inhibit release of inflammatory mediators. These drugs are generally avoided in children except as: (a) second-line drug for acute exacerbations in children > 5 years, and (b) adjunct therapy for control of nocturnal symptoms in moderate to severe persistent asthma.

  Being a drug with thin safety margin, IV Aminophylline therapy should be use cautiously, closely monitored with serum drug levels (<10 µg/ml). Loading dose should not be used in cases, who had received aminophylline in last 72 hours.
- ***Mast cell stabilizers,*** e.g. cromolyn sodium, nedochromil sodium, ketotifen, etc. prevent release of chemical mediators from sensitized mast cells on allergen exposure. These drugs are rarely used to prevent acute exacerbations but have no role in treatment of established attacks.
- ***Other drugs*** used in asthma include IV *magnesium sulphate*-a smooth muscle relaxant, used in acute exacerbations, and IV *Omalizumab* – an anti-IGE antibody, used for maintenance therapy in severe refractory asthma.

Aerosol therapy is a novel drug-delivery system, which has revolutionized the management of asthma. An *aerosol* is a suspension of the drug in gaseous medium, which is directly deposited in lower airways on inhalation via special devices.

TABLE 16.18: Common Anti-asthmatic medications in children

Drugs	*Doses*	*Side effects*
A. Selective β agonists		
Salbutamol	MDI/DPI 1–2 puff 4–6 hrly Neb: 0.15 mg/kg/dose PO 0.1 -0.2 mg/kg/d q8hr	Tremors, tachycardia Hypokalemia, hyperglycemia, Freon effect Long - acting salmeterol or Formometerol should never be used alone, always as inhalers in combination with ICS
Terbutaline	MDI 1–2 puffs 4–6 hrly PO 0.15 mg/kg/d q8hr	
Salmeterol	MDI/DPI 1–2 puffs 12–24 hrly	
Formoterol	MDI/DPI 1–2 puffs 12–24 hrly	
B. Anticholinergics		
Ipratropium bromide	MDI 1–2 puffs 8 hrly Neb: 0.5 mg/dose	Dry mouth, tachycardia
Tiotropium bromide	MDI 1–2 puffs 12 hrly	Only in children > 6 years
C. Steroids		
Beclomethasone*	**LD** 100–200, **MD** 200–400, **HD** >400 µg/day q12hr	Oral thrush, cough, dysphonia Growth failure ?
Budesonide*	**LD** 100-200, **MD** 200-400, **HD** >400 µg/day q12hr	
Fluticasone*	**LD** 50-100, **MD** 100-200, **HD** >200 µg/day q 12–24hr	
Hydrocortisone	IV 25–100 mg stat dose	None, short-term use
Prednisolone	PO 1–2 mg/kg/day q12–24hr	
D. Xanthine derivatives		
Aminophylline	IV 5 mg/kg (L) > 1 mg/kg/dose q6hr** PO 5–15 mg/kg/d q12hr	Tremors, seizures, tachycardia Toxic level > 20 µg/ml
E. Leukotriene receptor antagonists		
Monteleukast	PO 4 mg/day (2-5 yr) 5 mg/day (5-12yr) 10 mg/day (>12 yr)	Well tolerated except rare risk of "Churg-Strauss syndrome"
F. Mast cell stabilizers		
Sodium cromoglycate	1–2 puffs q 6-8hr	Reflex cough, bitter taste
Ketotifen	1 mg q12hr	Sedation, weight gain

*For children 6-11 yrs, Higher (Double) doses for adolescents > 12 years
LD: Low dose; **MD:** Medium dose; **HD:** High dose
**diluted 10 times in NS, infused over 15–30 minutes slowly. No loading dose, if received aminophylline in preceding 24 hours.

As only a particle size of <5 mm can cross mechanical airway barriers, <10–15% of inhaled drug reaches the lower airways by these devices. However, major benefits of this delivery system accrue from the fact that the drug is directly delivered at the target site with: (a) rapid onset of action, and (b) minimum side effects.

Aerosol devices may be: (i) *propellent driven*, e.g. metered dose inhalers (MDI), and (ii) *inspiration driven*, e.g. nebulizers or dry powder inhalers (DPI) (see Ch 32.5 for details).

Choice of the aerosol device depends on the age and cooperation from patient, as follows:

- *Nebulizer*, for acutely sick, breathless child, when large doses are to be delivered and child cannot cooperate.
- *MDI*, for domicilliary treatment in children >6 years, who can coordinate press-breathe act.
- MDI with a spacer, for domicilliary treatment in children between 3–6 years, who cannot co-ordinate, but can breath through a mouthpiece.
- *MDI with spacer and face-mask*, for children <3 years, who cannot breathe through a mouthpiece.
- *DPI for children >3 years*, who cannot coordinate, but can breath through a mouthpiece.

II. Management of Acute Exacerbation

Asthmatic exacerbations denote an acute or sub-acute deterioration in symptoms and airway obstruction from the baseline, usually following exposure to an external trigger, (e.g. upper respiratory infection, pollution) or poor adherence to controller medications. Most of these attacks can be managed at home and hospitalization is required only in severe/non-responding cases.

A. Home treatment should be based on a written individualized protocol and includes:

- Recognition of impending attack and assessment of its severity by PEFR. A PEFR of <80% of personal-best PEFR indicates acute attack (< 50% in moderate to severe attack).

- Use of inhaled SABA, i.e. salbutamol via MDI (100 mg/puff 4–10 puffs), every 20 minutes till response (max 3 doses).

  Single maintenance and reliever therapy (SMART) with combined inhaler of high-dose budesonide-formoterol (400/12 µg) with 2 puffs and repeat after 5 minutes) is preferred choice for acute exacerbation of asthma in children > 5 years, adolescents and adults.
- Reassessment for clinical response and PEFR improvement at the end of one hour:
  - *Good responders* (PEFR >80%, sustained for 4 hours) should continue SMART or inhaled SABA 4-hourly for next 2 days *and* double the dose of ICS, if taking.
  - *Partial responders or non-responders* should visit the hospital as early as possible.

B. Emergency hospital visit is needed for all children with unsatisfactory response to home treatment, though many of them can be sent back after 4–6 hours of observation after initial treatment, if response is satisfactory. Important steps in the management of acute asthmatic exacerbations in hospital are as follows **(Fig. 16.10)**:

Step I. Assessment of severity on admission on the basis of clinical features, PEFR and SaO_2. As per GINA guidelines 2023, asthmatic exacerbations in older children (5–12 years) are classified as *mild to moderate* ***or*** *severe* **(Table 16.19)**.

In younger children < 5 years, an exacerbation is considered as *severe* in presence of any of the following: (a) altered sensorium, i.e. agitated, confused or drowsy, (b) SaO_2 <92%, (c) inability to speak in phrases, (d) pulse rate >150–180 bpm, (e) RR > 40/minute, (f) cyanosis, and (g) silent chest (No wheezing).

Step II. First-hour management depends on the severity of attack and includes:

- *Oxygen therapy* with nasal prongs/mask to achieve a target SaO_2 of >94–98%. Immediate intubation and mechanical ventilation is needed in cases of impending respiratory failure.
- *Nebulized SABA*, e.g. *Salbutamol* (0.15 mg/kg diluted in 2 ml NS), every 20 minutes during first hour and then hourly till response. Inhaled Salbutamol delivered by MDI with spacer (4–10 puffs/20 minutes) is equally, if not more, effective alternative to nebulization. However, Spacer must be primed with at least 20 puffs before first use, to prevent sticking of the drug on the plastic body due to static charge.
- *Nebulized Ipratropium bromide* (250–500 µg/dose), every 20 minutes in first hour and than 2–4 hourly, in severe attacks on admission, though may be considered in mild to moderate attacks with poor response to SABA nebulizations in first hour.
- *First dose of systemic corticosteroids (rescue therapy)* as PO Prednisolone (1–2 mg/kg/day q8h) or IV. Hydrocortisone (50–100 mg/dose), irrespective of the severity of exacerbation.

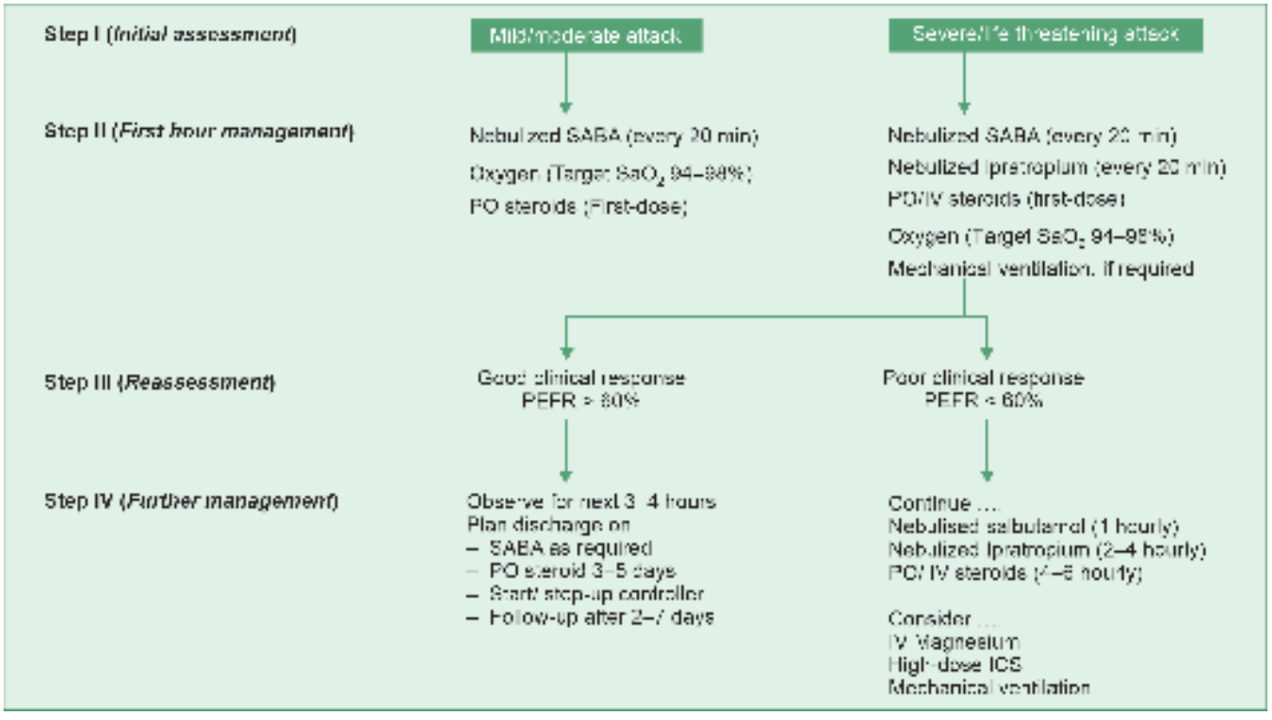


Fig. 16.10: **Emergency management of acute asthmatic exacerbation.**

Based on GINA Guidelines 2023

TABLE 16.19: Severity of acute asthmatic attack in children > 5 years of age*

Parameter	*Mild or moderate*	*Severe*
Talks in..	Phrases	Words
Preferred posture	Sitting	Sits hunch forward
Sensorium	Not agitated	Agitated
Respiratory rate	Increased	>30/min
Accessory muscles	Not in use	In use
Pulse rate (bpm)	≤120	>120
SaO_2	≥90%	<90%
PEFR (% Personal best)	≥50%	<50%
Presence of drowsiness, confusion and silent chest indicate life-threatening attack		

Source: GINA guidelines 2023.
*See text for assessment of severity in younger children < 5 years

- *IV magnesium sulphate* as a single infusion or high-dose ICS may be considered in selected severe exacerbations.

Step III. Reassessment of all patients at the end of one hour for clinical response and PEFR to decide further course of action. Response at this point is broadly classified as *Good* (PEFR >60%) and *Poor* (PEFR < 60%).

Step IVa. Management of good responders: Cases with good response at the end of one hour must be managed as follows:

- *Observe* for next 3–4 hours to exclude relapse of symptoms before discharge.
- *Continue PO Prednisolone* (1–2 mg/kg/d q8h), at home, for next 3–5 days.
- *Continue SABA* via MDI with spacer, at home, *as required, along with ICS* appropriate to the severity. SABA-only treatment at discharge is no longer recommended since the occurrence of exacerbation is a risk factor for future exacerbations.

  SMART with severity-appropriate ICS-Formoterol is preferred on discharge to reduce the risk of further exacerbations.
- *Counsel* regarding adherence to therapy, avoidance of exacerbations and early recognition of the attack.

Step IV b. Management of poor responders: Cases with poor response at the end of first hour are in *status asthmaticus* and need to be hospitalized, if necessary in intensive care. Hospitalization is also recommended to all children with—(a) severe or life-threatening attack, (b) past history of multiple exacerbations requiring oral steroids or emergency room visits, and (c) unreliable management at home. Important steps in the management of poor responders to first-hour management include:

- *Continuous oxygen* support and mechanical ventilation, if respiratory failure supervenes. Role of helium oxygen therapy or non-invasive ventilation is unclear.
- *Continue nebulized SABA*, e.g. Salbutamol 1-hourly (or as continuous nebulization) along with *Nebulized Ipratropium bromide* 2–4 hourly. If necessary, both drugs can be mixed together (Duolin®) in same solution.
- *Continue systemic steroids* as IV hydrocortisone (50–100 mg every 6-hourly) till switch-over to oral steroids is possible.
- *IV magnesium sulfate* may be used in refractory cases as single infusion of 40–50 mg/kg, over 20 minutes.
- *IV aminophylline* is not recommended in routine management of asthma exacerbations due to poor efficacy and safety profile. However, it may be used in very refractory cases as IV aminophylline 5 mg/kg (loading dose), dissolved 10 times in normal saline and infused slowly over 10–15 minutes, followed by 1 mg/kg 6-hourly. *Loading dose should not be given in cases who have received aminophylline in last 72 hours.*
- Antibiotics are not routinely indicated, unless there is definite evidence of infection. LTRA and LABA have no role in management of acute asthma and sedatives are contraindicated.

Patients, who improved with these measures, must be stepped down to step II of management before considering the discharge as per step *IVa*.

III. Step-wise Long-term Management of Asthma

Long-term control of asthma aims to-(a) achieve good control of symptoms, and (b) minimize future risk of asthmatic exacerbations and involves:

- Initial assessment of the level of symptom control and risk of future exacerbations;
- Initiation of appropriate pharmacotherapy based on the initial assessment;
- Regular monitoring at home and periodic assessment at hospital, for the level of symptom control, adherence to the treatment and adverse effects of medications.
- *Step-wise* modifications in pharmacotherapy, according to the level of control.
- Preventive interventions, e.g. avoidance of triggering agents, immunotherapy and non-pharmacological methods.

A. Initial assessment: While acute exacerbation may be the first presentation of asthma in children, many cases present without current symptoms but with suggestive past history. Once the diagnosis of asthma has been made and the acute exacerbation has been controlled, all cases must be classified according to:

- Level of asthma symptom control as—(*a) well-controlled, (b) partly-controlled, and (c) uncontrolled* **(Table 16.20)**.
- Presence or absence of risk factors for future exacerbations as follows:
  - Uncontrolled asthma symptoms,
  - One or more severe exacerbations in previous year,
  - Start of the child's usual flare-up season
  - Exposure to potential allergens/triggering agents, e.g. smoke, allergens, etc. and

TABLE 16.20: Asthma symptom control classification

Parameter	*Controlled*	*Partly controlled (Any one)*	*Uncontrolled (Three or more)*
Day-time symptoms	<2 /week	>2/week	>2/week
Night-time symptoms	None	Any	Any
Activity limitation	None	Any	Any
Need for reliever Rx	<2/week	>2/week	>2/week

Modified from GINA Guidelines 2023.

- Major psychological or socioeconomic problems
- Poor adherence with controller medications
- Co-morbidities, e.g. obesity, sinusitis

B. Initiation of appropriate pharmacotherapy involves use of maintenance medications at appropriate level of severity based on initial assessment regarding level of asthma symptom control and future risk of exacerbations. **Table 16.21** provides preferred choices and alternative options for maintenance therapy, which differs in children above 6 years and in younger children *In addition, intermittent use of SABA, e.g. MDI Salbutamol (100 µg) is necessary during acute exacerbations.*

C. Regular assessment and monitoring must include daily home monitoring and periodic asthma-clinic follow-ups. All asthmatic children or their parents should keep a daily record of symptoms and PEFR at home and must be trained to: (a) recognize an acute exacerbation and its home management, and (b) to make minor modifications in controller therapy. All patients must also be followed up at least every 3 months in asthma clinic to assess the level of control and modify therapy. Follow-up after 7 days of acute exacerbation is advised in cases visiting emergency room or needed hospitalization.

D. Stepping-up and stepping-down of controller therapy depends on the periodic assessment with following general principles:

- *Stepping-up* of therapy is required any time, after observation of clinical response and inter-attack PEFR. As a thumb rule, need for reliever SABA on daily basis indicates poor long-term control and need for step-up therapy. *Short-term step-up* for 1–2 weeks may be required in otherwise controlled cases following during viral infections or potential allergen exposure.
- *Stepping-down* of therapy to a lower step is advised only after minimum 3 months of control.

E. Preventive interventions include avoidance of triggering agents, immunotherapy and non-pharmacological methods.

- ***Avoidance of allergens/triggering agents*** is often difficult and impractical in children, though following precautions may be helpful:
  - Early recognition of viral infections, e.g. URTI and stepping-up of inhaled steroids or short-term use of oral steroids, to prevent exacerbation.
  - Avoidance of allergens, as discussed in Chapter 8.4.1. Avoidance of many dietary items is often overemphasized, without scientific basis. However, a proven cause-effect observation with particular

TABLE 16.21: Step-wise pharmacotherapy of asthma in children (GINA Guidelines 2023)

Step	*I*	*II*	*III*	*IV*	*V*
Asthma Control	Well controlled	Partly controlled	Partly controlled	Uncontrolled	Uncontrolled
Future risk	None	Present	None	present	–
Maintenance therapy > 5 years age					
Preferred	LD-ICS (SOS)	LD-ICS	LD-ICS + LABA, or MD-ICS, or Very LD-ICS*+F	MD-ICS+LABA SMART	Refer + HD-ICS+LABA Add-on Rx*
Alternatives	LD-ICS	LD-ICS or LTRA	LD-ICS + LTRA	+Tiotropium/LTRA	LD-OCS
Maintenance therapy > 5 years age					
Preferred	–	LD-ICS or LTRA	LD-ICS (Double dose)	Refer LD-ICS (Double dose)	
Alternatives	LD-ICS (SOS)	LD-ICS (SOS)	LD-ICS + LTRA	Add LTRA *or* ↑ ICS frequency *or* Add ICS (SOS)	
Reliever therapy					
SABA as required					

LD-ICS: Low-dose inhaled corticosteroids (100–200 µg/dose); **MD-ICS:** Medium-dose inhaled corticosteroids (200–400 µg/dose); **HD-ICS:** High-dose inhaled corticosteroids (>400 µg/dose); **LD-OCS:** Low-dose Oral Corticosteroids; **LTRA:** Leukotriene receptor antagonist; **LABA:** Long-acting β-agonist, e.g. Formometerol or Salmeterol; **SABA:** Short actingβ-agonist, e.g. Salbutamol; **SMART:** Single maintenance and reliever therapy; **Very LD-ICS+F** (Budesonide+Formoterol100/6 µg) or LD-ICS+F (Budesonide+Formoterol 200/6 µg)
*Add-on treatment includes anti-IgE antibody, very rarely used in children.

foodstuff may be an indication to avoid it. Canned foods with preservatives, coloring agents, etc. Should be avoided.
  - Avoidance of triggering factors, e.g. passive smoking, strenuous exercise or drugs, e.g. aspirin.
  - Diagnosis and treatment of co-existing illnesses, e.g. *gastro-esophageal reflux*, sinusitis, tuberculosis, etc.
- ***Immunotherapy,*** i.e. desensitization of the child to identified allergen (Chapter 8.4.1) is often unrewarding, though may be tried in selected cases of severe persistent asthma, where avoidance of identified allergen is not possible.
- ***Non-pharmacological approaches*** in long-term control of asthma include *yoga* therapy in older children, *behavioral modification* and *patient education*.

Outcome: While the natural course of asthma is unpredictable, most cases (>60%) become relatively symptom-free by the end of puberty due to growth of airways, less incidence of precipitating viral infections, better awareness about trigger factors and, probably auto-desensitization. However, many cases recur in later life, especially those with following risk factors: (a) family history of atopy, (b) late onset disease, i.e. after 3 years of age, (c) severe disease with poor lung functions in childhood.

Difficult to control asthma is a term is used to denote cases, who do not respond well despite appropriate controller therapy, usually due to presence of co-morbidities, poor adherence to treatment and constant allergen exposure. All these cases must be reviewed for these factors with appropriate remedial measures. However, some cases do not respond even after that and referred as "*Refractory asthma*". Management of them is best left to the experts.

16.9 PNEUMONIA

Pneumonia, i.e. *inflammation of lung parenchyma, due to infectious or non-infectious etiology,* may be broadly classified as *Infective* or *non-infective* pneumonias.

16.9.1 INFECTIVE PNEUMONIA

Acute infective pneumonia is the commonest cause of hospitalization and mortality in under-5 children of India, responsible for ~20% deaths in this age group.

Etiology: According to the source of infection, these cases may be classified as *community-acquired* pneumonia or *nosocomial* pneumonia **(Table 16.22)**.

- ***Community-acquired pneumonia*** is predominantly viral (50%) or bacterial (40%) in origin.

  Viral pneumonia may be caused by specific respiratory viruses, e.g. RSV, influenza, parainfluenza, adenoviruses, etc. or as a part of generalized exanthematous illnesses, e.g. measles or varicella.

TABLE 16.22: Common causes of pneumonia

Community-acquired pneumonia
- *Newborns: Staph. aureus, E. coli,* Klebsiella, GBS
- *Infants:* Hib, *Staph. aureus, S. pneumoniae,* viruses
- *Pre-school: S. pneumoniae, S. pyogenes,* Hib, viruses
- *School: Myco. pneumoniae, S. pneumoniae,* viruses

Nosocomial pneumonia
- *Gram negative:* Klebsiella, Pseudomonas
- *Gram positive: Staph. aureus,* CONS
- *Fungal,* e.g. candidiasis

Opportunistic infections
- *Pneumocystis carinii*
- *Fungal:* Candidiasis
- *Viruses:* CMV

Hib: *H. influnzae* B; **CONS:** coagulase negative staphylococci; **GBS:** Group B streptococci

Bacterial pneumonia may be primary or superimposed on viral or non-infective pneumonia. Etiology of bacterial pneumonia depends on the age as well as microbial pattern in the community.

- ***Nosocomial pneumonia*** are usually gram negative, with Klebsiella and Pseudomonas as leading pathogens, though staphylococcal and fungal infections are also common.
- ***Opportunistic infections***, e.g. coagulase negative staphylococci (CONS), candida or *Pneumocystis jirovecii*, are common in immunocompromised children.

Epidemiology: Community-acquired pneumonias are acquired as droplet infection from a case/carrier of the organism, though hematogenous spread from distant septic focus is common in newborns or debilitated children. Nosocomial infections may originate from any animate or inanimate source in the hospital.

Risk factors for recurrent pneumonia in childhood include:

- Environmental factors, e.g. over-crowding, pollution, passive smoking, etc.
- Nutritional deficiencies, e.g. malnutrition, vitamin A deficiency.
- Recurrent aspiration, e.g. cleft-palate, gastroesophageal reflux, bulbar palsy.
- Immunodeficiency, e.g. AIDS, primary immunodeficiency disorders.
- Increased pulmonary vascularity, e.g. in congenital heart defects.
- Chronic lung disease, e.g. asthma, cystic fibrosis.
- *Others:* Low birth weight, top feeding.

Pathologically, pneumonia may be classified according to predominant tissue involvement as: (a) *bronchopneumonia*, e.g. *Staph. aureus*, (b) *lobar pneumonia*, e.g. *S. pneumoniae*, (c) *interstitial pneumonia*, e.g. viral or mycoplasma infections, and (d) *destructive pneumonia* involving all pulmonary elements, e.g. pseudomonas or Hib pneumonia.

Clinical presentation varies according to the etiology, though general features include:

- Preceding history of upper respiratory infection or exanthematous illness.
- Acute, rapidly progressive course in most cases, though viral, mycoplasma or Hib pneumonias run relatively insidious course.
- *Symptoms*: Fever, cough and respiratory distress with tachypnea, dyspnea, feeding difficulties, grunting and cyanosis. Fever is more prominent in bacterial pneumonia. Presence of chills indicates probable pneumococcal etiology.
- *Clinical signs* depend on the extent of lesion and vary from diffuse crepitations (*bronchopneumonia)* to signs of consolidation, e.g. dull percussion note, increased vocal resonance/fremitus, and bronchial breathing (*lobar pneumonia)*. Signs are disproportionately less and fluctuating in interstitial pneumonia. Nuchal rigidity may be present in right apical pneumonia.
- *Complications*, e.g. empyema, pneumothorax may complicate clinical picture in many cases.

Diagnosis of pneumonia *per se* depends on clinical and radiological findings **(Table 16.23, Fig. 16.11)**, though etiological confirmation requires:

- Direct detection of organisms on smear, culture or PCR from body fluids, e.g. sputum, gastric aspirate, bronchoalveolar lavage, pleural fluid, etc.
- Serological investigations for viral antigen or atypical pneumonia.

Other investigations, e.g. blood gas analysis, etc. are necessary to assess and monitor the severity of disease.

D/D: Important differentiating features between bacterial, vial and mycoplasma pneumonia are given in **Table 16.24**.

Bacterial pneumonia: Presence of polymorphonuclear leukocytosis and elevated CRP or procalcitonin values support bacterial etiology. Special characteristics of some common causes are as follows:

- ***Staphylococcal pneumonia*** is most common in infants, toddlers or debilitated children with septic foci, e.g. pyoderma, otitis, etc., acquired via hematogenous route. Clinical course is usually acute and rapidly progressive, with diffuse bronchopneumonia and development of *pneumatoceles* (thin-walled air cavities) on chest X-ray **(Fig. 16.11E)**. Complications are common and include—(a) empyema, (b) pneumothorax, (c) distant metastatic infections, e.g. meningitis, and (d) residual lung lesions, e.g. bronchiectasis, lung abscess, etc.
- ***Pneumococcal pneumonia*** is primarily alveolar, with four pathological stages-exudation > red hepatization > gray hepatization > resolution. Apart from being commonest community-acquired pneumonia in 1–5 years age group, children with splenic dysfunction, e.g. sickle cell disease, asplenia, splenectomy, etc. or nephrotic syndrome are relatively more prone for pneumococcal pneumonia.

  Clinico-radiological signs may vary from localized *lobar pneumonia* in older cases to diffuse *bronchopneumonia* in infants **(Fig. 16.11A and B)**. Presence of chills, abdominal pain due to basal pleuritis and nuchal rigidity due to apical lesions strongly indicates pneumococcal etiology.
- ***H. influenzae B (HiB) pneumonia*** is most common between 3 months to 2 years of age. It is usually lobar pneumonia with destruction of airway epithelium and marked interstitial and alveolar edema. Most cases run relatively insidious course, frequently associated with otitis media and plural effusion. Extrapulmonary complications, e.g. meningitis, arthritis, pericarditis, etc. are more common than pulmonary complications. Incidence of Hib is expected to decline in recent years after universal Hib immunization.
- ***Streptococcal pneumonia*** is most common in 3–5 years age group, usually after an exanthematous illness or sore throat. Being an interstitial pneumonia, clinical signs are disproportionately less than the dyspnea. Large pleural effusions are common.
- ***Gram-negative pneumonia*** are usually *nosocomial* in origin, seen in newborns, sick or immunocompromised children or those with pre-existing lung disease. Fulminant and therapy-resistant course with septicaemia is common. *Pneumatoceles and apical consolidation with bulging borders on X-ray is common in Klebsiella* pneumonia.

Viral pneumonias, more common in winter season, are predominantly *interstitial* pneumonias with *disproportionately less lung signs than the respiratory distress*. Chest skiagram reveals characteristic diffuse infiltrates with hyperinflation or transient lobar infiltrates **(Fig. 16.11C)**. Diagnosis is largely empirical, based on epidemiological pattern and sterile bacterial cultures. Viral serology is unreliable for early diagnosis.

TABLE 16.23: D/D X-ray picture of pneumonia

X-ray findings	*Probable diagnosis*
Lobar consolidation	*Pneumococci*
Pneumatoceles/abscess	*Staph. aureus, Klebsiella*
Large effusion	*Streptococci*
Empyema/pneumothorax	*Staph. aureus*
Ground-glass (interstitial)	*Viral, mycoplasma*
Miliary mottling	*TB, PCP, TPE*
Upper lobe consolidation	*Aspiration, Klebsiella**
Lower lobe consolidation	*Foreign body*

*with bulging fissure **(Fig. 16.11f)**. **TPE**: Tropical pulmonary eosinophilia

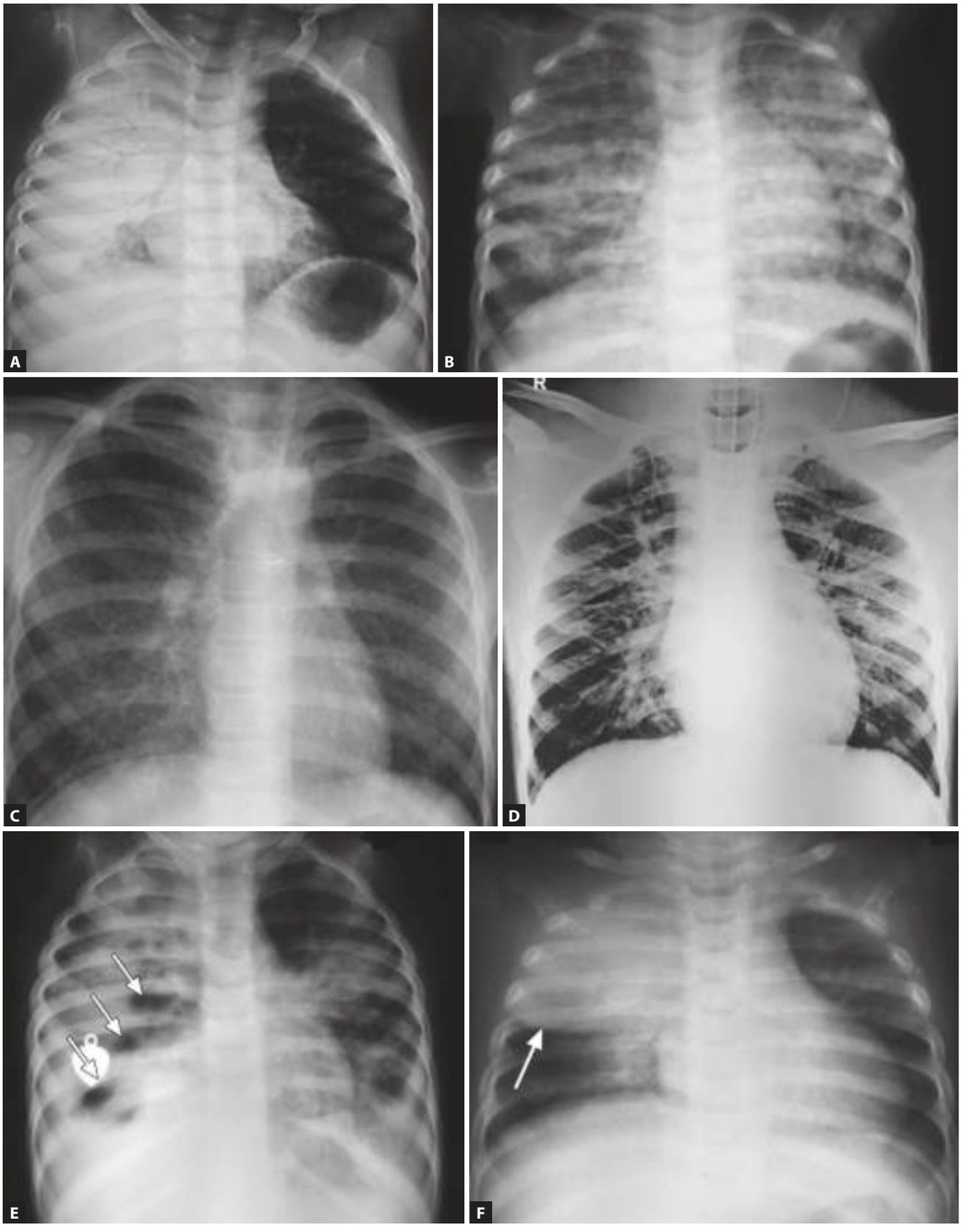


Fig. 16.11: **Representative X-ray chests in various types of pneumonia.**
(A) Lobar pneumonia; (B) Bronchopneumonia; (C) Interstitial pneumonia; (D) Aspiration pneumonia; (E) Staphylococcal pneumonia with pneumatoceles; (F) Klebsiella pneumonia with bulging fissure.

TABLE 16.24: D/D bacterial, viral and mycoplasma pneumonia

	Bacterial	*Viral*	*Mycoplasma*
Common age	<5 years	<5 years	>5 years
Onset/course	Acute	Insidious	Insidious
Season pattern	No	Yes	No
Fever/toxicity	+++	+	+
Cough	Productive	Dry	Dry
Lung signs	+++	+	+
X-ray	+++	+	++
Cultures	+	–	–

Antiviral therapy with oral Oseltamivir is recommended in all cases of Influenza-like illness (ILI) with Category B and C disease (Ch 10.26), while nebulized ribavarin (RSV) is recommended only in cases with chronic lung or heart disease. Bronchiolitis obliterans is an important late complication of viral pneumonia.

Giant cell pneumonia with typical giant cells containing inclusion bodies-*Hetch cells*, is occasionally seen in subclinical measles infection or after measles vaccination in immunocompromised children.

Atypical pneumonia denotes a heterogeneous group with milder course, minimum lung signs and sterile bacterial cultures. Common causes of atypical pneumonia include—mycoplasma, chlamydia and legionella infections.

- ***Mycoplasma pneumoniae*** *(primary atypical pneumonia)* is the *commonest cause of community-acquired pneumonia in school-children (5–12 years)*, presenting as interstitial pneumonia of gradual onset after preceding upper respiratory tract infection. Clinical signs are disproportionately less than X-ray findings, which reveal extensive and diffuse fluffy exudates with hilar lymphadenopathy.

  Diagnosis usually rests on elevated cold agglutinin titers (>1:64) or positive IgM-ELISA test. Confirmation by throat/sputum cultures or PCR is not possible. Complications are rare and include *autoimmune illnesses*, e.g. Steven-Johnson syndrome, acute transverse myelitis, Guillain-Barre syndrome and hemolytic anemia.
- ***Chlamydia pneumoniae*** is an emerging cause of community-acquired pneumonia in school children. Diagnosis usually rests on serology (IgM >1:16). Tissue cultures from nasopharynx, sputum or bronchial lavage are confirmatory but rarely available.
- ***Legionnaire's pneumonia*** is an emerging cause of atypical nosocomial pneumonia in immunocompromised children. Legionella is an intracellular parasite, which grows inside the protozoans present in water tanks/pipes and infection is acquired on ingestion or inhalation of contaminated water or aerosols. Extrapulmonary manifestations, e.g. hepatorenal dysfunction and CNS involvement are common. Erythromycin with/without rifampicin is the drug of choice in these cases.

Management of pneumonia includes supportive as well as specific antimicrobial therapy. Hospitalization is indicated in: (a) young children <6 months, (b) moderate to severe respiratory distress, (c) toxic appearance, (d) poor oral intake or vomiting, (e) immunocompromised children, (f) complicated pneumonia, e.g. presence of empyema, and (f) no response to domiciliary antibiotic therapy.

A. Specific therapy: Choice of empirical antimicrobial therapy on admission depends on the age, severity and local experience with antibiotic resistance **(Table 16.25)**, which should be modified after culture reports or in cases with unsatisfactory therapeutic response.

Antibiotics should be continued until the patient is afebrile for 72 hr for minimum 10 days in uncomplicated pneumonia. Shorter duration may be used in patients treated on OPD basis or by Azithromycin.

TABLE 16.25: Antimicrobial therapy in pneumonia

Empirical therapy on OPD basis (PO)	
< 5 yr age	Amoxycillin* *or* Co-amoxclav *or* Cefuroxine
> 5 yr age	Azithromycin *or* Levofloxacin (adolescents)
Empirical therapy in hospitalized cases (IV)**	
< 3 mo age	Ceftriaxone or Cefotaxime + Aminoglycoside
3 mo – 5 yrs	Ampicillin or Ceftriaxone or Cefotaxime or co-amoxclav
> 5 yrs age	Ceftriaxone or Cefotaxime with Azithromycin
Empirical therapy in nosocomial pneumonia	
IV Ceftazidime or Ceftriaxone **with** Aminoglycoside	
Organism-specific therapy (IV or PO)	
S. pneumoniae	Penicillin G or Cefotaxime or Ceftriaxone
S. pyogenes	Penicillin G or Ampicillin
Staph. aureus	Ceftriaxone/coamxoclav with Cloxacillin/ Vancomycin
H. influenzae	Ceftriaxone or Cefotaxime
Mycoplasma	Azithromycin or Clarithromycin or Levofloxacin
Chlamydia	Azithromycin or Clarithromycin or Levofloxacin
Pseudomonas	Ceftazidime or Piperacillin + Aminoglycoside
E.coli/Klebsiella	Cefotaxime + Aminoglycoside

*Higher dose of amoxicillin upto 90 mg/kg/day are recommended in high-resistance populations for Pneumococci.
**Cloxacillin, vancomycin or Clindamycin for suspected Staph. pneumonia

Presently, empirical antiviral therapy with oral Oseltamivir is recommended in all cases of influenza-like illness (ILI) with Category B and C disease (Ch 10.26), due to ongoing pandemic.

B. Supportive therapy includes:

- Fluid and electrolyte correction and maintenance.
- Monitoring for progressive respiratory distress clinically and by pulse oximetry. Sedatives are contraindicated and may mask clinical signs.
- Respiratory support, including humidified oxygen, continuous positive airway pressure (CPAP) or non-invasive/invasive mechanical ventilation.
- Management of co-existing sepsis or circulatory shock.
- Treatment of pulmonary (empyema/pneumothorax) or extrapulmonary complications.
- Symptomatic treatment for fever, cough, etc. Oral zinc 10–20 mg/day has been shown to reduce mortality in clinically defined severe pneumonia in developing countries.

16.9.2 NON-INFECTIVE PNEUMONIA

Non-infective pneumonias denote alveolar inflammation due to *chemical* (aspiration), *allergic* (hypersensitivity) *or physical* injury (smoke). However, most of them are rapidly complicated by superadded infections.

Aspiration pneumonia: Clinical presentation of aspiration pneumonias depend on the type of aspirate, e.g. (a) gastric contents/oral feeds, e.g. milk, (b) volatile hydrocarbons, e.g. kerosene and (c) thick viscous lipoid substances, e.g. oils, discussed as follows:

Milk-aspiration syndrome: Aspiration of milk/gastric content is common in infants or debilitated children with following risk factors—(a) oropharyngeal defects, e.g. cleft palate, (b) esophageal problems, e.g. strictures or gastroesophageal reflux, (c) neuromuscular incordination in preterms, comatose or floppy child, and (e) severe respiratory distress.

Clinically, these cases present with a *biphasic course*- (a) immediate bouts of cough or apnea (choking) due to mechanical obstruction or reflex laryngospasm, followed by; (b) a silent phase of 1–2 hours; and then (c) progressive respiratory distress due to chemical pneumonitis and secondary infection.

Signs of pneumonia appear only after 1–2 hours of aspiration with development of crepitations/rhonchi, etc. Presence of high fever indicates secondary infection.

Diagnosis rest on-(a) history of vomiting/choking during feeds, (b) presence of vomitus/milk on immediate airway suction, and (c) bilateral perihilar or diffuse reticular infiltrates on chest X-ray *after 2 hours* of aspiration **(Fig. 16.11E)**. Immediate X-ray may be normal.

Management includes—(a) immediate endotracheal suction, (b) oxygen or ventilatory support, (c) fluid and electrolyte therapy, (d) antibiotics-Penicillin/clindamycin with an aminoglycoside to cover anaerobic oral flora or gram-negative hospital flora. Role of prophylactic antibiotics is controversial. *Steroids are contraindicated.*

Prognosis depends on severity of underlying disease and quantum of aspiration, with immediate mortality of ~25%. In survivors, clinical and radiological signs resolve in next 10–14 days.

Hydrocarbon pneumonia: Accidental ingestion of hydrocarbons, e.g. kerosene, petrol, turpentine, etc. is a common cause of poisoning in rural Indian children, specially toddlers (1–3 year).

Pathogenesis: While actual quantity of ingestion is usually very small due to unpleasant taste, these low viscosity volatile fluids easily trickle down the airways to—(a) destroy pulmonary surfactant (atelectasis), (b) initiate inflammatory reaction (pulmonary edema), followed by (c) secondary infection (pneumonia).

Clinical manifestations may not correlate with quantum of aspirate and include—(a) immediate bouts of cough/vomiting, followed by (b) a silent phase for ~6–12 hours and then, (c) progressive development of pulmonary edema. Development of high fever suggests secondary pneumonia.

Lung signs are often disproportionately less than X-ray abnormalities. Signs of systemic toxicity, e.g. seizures and coma are rare and usually indicate hypoxic injury rather than direct substance toxicity.

Diagnosis depends on history and chest skiagram, which should be delayed for minimum 6 hours after ingestion to allow development of radiological signs, e.g. pulmonary edema (early) or extensive infiltrates, patchy atelectasis and consolidation (late). Air-leaks, e.g. pneumothorax or subcutaneous emphysema are common.

Management includes:

- No immediate intervention is needed in most cases and *nasogastric lavage or induction of emesis is contraindicated due to fear of aspiration, except* in cases with ingestion of hydrocarbon solvents with toxic substances, e.g. organophosphorus compounds and presenting within 2 hours. In such cases, gastric lavage may be necessary to minimize absorption, but should be done only after insertion of a cuffed endotracheal tube to prevent aspiration.
- Close observation for next 6 hours, followed by chest X-ray to exclude developing pneumonia. (No patient must be sent home before 6–12 hours of observation).
- Hospitalization of symptomatic cases with supportive therapy, e.g. O_2 or ventilatory support and chest physiotherapy. Development of ARDS necessitates positive-pressure ventilation, though many workers suggest early intubation to prevent progressive

CNS depression. Bronchodilators, e.g. salbutamol nebulizations may be used in select cases.

- Prophylactic antibiotics are not routinely indicated, except in symptomatic cases with possible secondary infection. *Steroids are contraindicated.*

Prognosis depends on—(a) volume of ingestion, (b) age of patient, (c) severity of lung signs and (d) efficacy of treatment, with overall mortality of <5–10%. Most cases recover after stormy course within a week.

Lipoid pneumonia is a chronic, interstitial pneumonia due to aspiration of high-density oils, e.g. oily nasal drops, drugs (cod liver oil), feeds (ghee) or petroleum jelly. Indian custom of instilling massage oil in nostrils and ears during early infancy is an important risk factor for lipoid pneumonia.

Pathologically, development of lipoid pneumonia evolves through three stages: (a) initial interstitial proliferative and exudative inflammation, followed by (b) diffuse fibrosis or secondary infection, and lastly, (c) formation of multiple nodules, i.e. *paraffinomas*.

Clinically, most cases are initially asymptomatic and present after many months with persistent cough, progressive dyspnea and recurrent chest infections.

Diagnosis rests on history and characteristic X-ray appearance, i.e. *bilateral perihilar densities, radiating from hilum in a fan-like manner.*

Management is non-specific with treatment of intercurrent infections and prognosis is guarded due to progressive lung pathology.

Hypersensitivity pneumonia, also termed *hypereosinophilic lung syndromes* often mimics asthma (wheezy child), due to bronchial/pulmonary reaction to a known/unknown allergen. Eosinophilia and raised IgE levels is common. Some common hypersensitivity pneumonias are as follows:

Loeffler syndrome is a pulmonary hypersensitivity reaction to many antigens/allergens, e.g. (a) worm infestations, e.g. ascaris, toxocara, etc., or (b) drugs, e.g. aspirin, sulfonamides, penicillin, etc.

These cases presents as a chronic disease with-(a) paroxysmal attacks of cough, wheezing, dyspnea without fever, (b) transient, generalized pulmonary infiltrates (miliary mottling), and (c) eosinophilia. Treatment includes wormicidal agents and supportive bronchodilator therapy during attacks.

Tropical pulmonary eosinophilia is a hypersensitivity reaction to microfilariae, characterized by—(a) paroxysmal cough, wheezing and dyspnea, (b) absolute eosinophil count >2000/ml, and (c) presence of microfilariae or anti-microfilarial antibodies in blood. Chest skiagram is normal or reveals miliary mottling.

Treatment may be started empirically in endemic regions with PO Diethylcarbamazine 5 mg/kg/day for 14–21 days, which may be repeated in partially responsive cases. Response is monitored clinically and by serial eosinophil counts. (Ch 10.35)

Allergic bronchopulmonary aspergillosis (ABPA) is the hypersensitivity response to inhaled *aspergillus* spores, usually in children with chronic lung diseases. These cases present with recurrent cough/wheeze with occasional expectoration of pathognomonic brown plugs in sputum. Chest X-ray may reveal proximal bronchiectasis.

Diagnosis is supported by positive skin allergen test or presence of aspergillus-specific IgE antibodies. Total IgE levels usually exceed >1000 ng/ml.

Low-dose steroids (PO prednisolone 0.5 mg/kg/d) for 4–8 weeks is the treatment of choice, along with specific anti-fungal therapy.

Smoke injury: Thermochemical injury to respiratory mucosa is an important cause of morbidity and mortality in burns, due to inhalation of soot (thermal injury) or noxious gases, e.g. carbon monoxide (chemical injury).

Clinical presentation depends on duration and severity of exposure and may be divided into four stages:

a. Immediate respiratory distress during first 8–12 hours due to bronchospasm, laryngeal edema and alveolar exudation, which must be treated with IV steroids and endotracheal intubation/tracheostomy, if necessary.
b. Pulmonary edema after 8–12 hours, treated with diuretics, fluid restriction and ventilatory assistance.
c. Secondary infection after 4–5 days, usually caused by *Staph. aureus* or Pseudomonas and treated with antibiotics.
d. Cervical eschar formation with constriction of airways after 3–5 days, in cases with full thickness burns of respiratory mucosa. It needs to be treated with bronchoscopic vertical division of burn crust, if necessary.

Carbon monoxide poisoning and asphyxia may also lead to CNS changes, i.e. irritability, visual impairment, altered sensorium and occasionally, coma.

Management depends on clinical staging (discussed earlier), though even asymptomatic cases should be observed for 24 hours after exposure to smoke/fire, for signs of smoke injury or Carbon monoxide poisoning.

Acute Respiratory Infections (ARI) Control Program

Considering the fact that—(a) ARI account for ~20% mortality in under-five children, and (b) diagnosis and differentiation of viral and bacterial ARIs is often difficult in resource limited settings, National ARI Control Programme was launched in 1989, to focus on the clinical-approach based management of these cases, as per WHO guidelines.

It is currently a component of comprehensive *RMNCH+A strategy* (reproductive, maternal, neonatal, child and adolescent health) of National Health Mission, implemented through existing health infrastructure using Integrated management of Neonatal and Childhood Illness (IMNCI) guidelines (Ch 29).

Under IMNCI guidelines, a child aged 2 months-5 years with respiratory illness is classified as:

- ***No pneumonia*** (cough and cold), in absence of fast breathing or other following signs, who can be treated at home with home remedies without antibiotics and follow-up after 5 days.
- ***Pneumonia*** with respiratory rate >50 in infants or >40 in older children, who should be treated with PO Amoxycillin 40–50 mg/kg/d q8–12 hr for 5 days and follow-up after 2 days.
- ***Severe pneumonia*** with lower chest indrawing, central cyanosis or any danger sign, i.e. inability to feed, seizure, coma or vomiting, should be immediately referred for hospitalization after a dose of IM antibiotics.

This classification does not apply to children < 2 months, who should be immediately referred for hospitalization in presence of any signs of severe disease.

Major component of ARI control program are—(a) to train paramedical staff at the community level for early diagnosis and appropriate treatment/referral of ARI cases, using standard case management guidelines, (b) to encourage rational treatment practices while limiting the irrational use of antibiotics, and (c) to prevent predisposing illnesses for pneumonia, e.g. measles, pertussis and diphtheria by effective immunization.

16.10 CHRONIC LUNG DISEASES

While tuberculosis is the commonest chronic lung disease in Indian children, this section deals with some other important chronic lung disorders of congenital or acquired origin.

16.10.1 BRONCHIECTASIS

Bronchiectasis is a chronic suppurative lung disease, characterized by '*permanent dilatation of the subsegmental airways,* due to inflammatory destruction of bronchial/peribronchial tissue and accumulation of infected material in dependent bronchi'.

Etiopathogenesis: *Persistent infection* and/or *bronchial obstruction* are two important events in bronchiectasis. Whole pathology may be initiated by:

- *Primary infective lesions*, leading to bronchiolar destruction and secondary dilatation in:
  - Airway infections, e.g. bronchitis, cystic fibrosis.
  - Parenchymal infections, e.g. pneumonia, pertussis, measles.
  - Recurrent aspirations and infections, e.g. in GERD, cleft palate, etc.
  - Immunodeficiency states
- *Primary obstructive lesions* with bronchial dilatation, distal collapse and secondary infection in:
  - *Intrabronchial* foreign body, mucus plug, etc.
  - *Extrabronchial* lymph nodes, tumors, etc.
  - Functional obstruction, e.g. bronchomalacia, etc.
- *Congenital bronchiectasis* is seen in:
  - *Kartagener syndrome, (*bronchiectasis, sinusitis and situs inversus).
  - Cystic diseases of the lung.

Tuberculosis and foreign body aspiration are two leading causes of bronchiectasis in Indian children, while cystic fibrosis dominates in developed countries.

Pathologically: Bronchiectasis is characterized by-(a) loss of normal ciliated epithelium in bronchi with peribronchial inflammation, (b) thickening and cystic dilatation of bronchi that may be cylindrical, fusiform or secular, and (c) obstructive endarteritis and multiple abscesses.

Right lower-lobe bronchiectasis is common following foreign body aspiration, while tuberculosis usually involves right middle lobe due to bronchial compression by hilar lymph nodes.

Clinical presentation is usually insidious with waxing and waning course. Preceding history of pneumonia, foreign body aspiration or asthma is common. Important clinical features include:

- *Persistent wet cough* with copious mucopurulent sputum, more prominent in morning due to change of posture causing movement of the mucus and mucosal irritation. Intermittent blood-streaked sputum or frank hemoptysis is not uncommon.
- *Failure to thrive* and *clubbing.*
- Respiratory finding, often limited to coarse crepitations or signs of atelectasis.

Diagnosis should be suspected in any case with chronic lung disease and clubbing, confirmed by:

- *X-ray chest*, showing characteristic *honeycomb appearance* with/without collapse and multiple small abscesses **(Fig. 16.12)**.
- High-resolution CT scan, which is the gold standard for diagnosis as well as to assess the status of other lung, before surgery. Findings may vary according to pathological type, e.g. *tram-lines* or *signet-ring* appearance in cylindrical disease, *beaded bronchi* in varicose disease and cystic *strings and clusters* in saccular disease.
- *Sputum examination,* which is usually seropurulent and separates in 3 layers after few hours-a thin serous layer on top, a fibrinous layer in middle and a cellular layer at the bottom of sample (*three-layer test*). Direct gram/

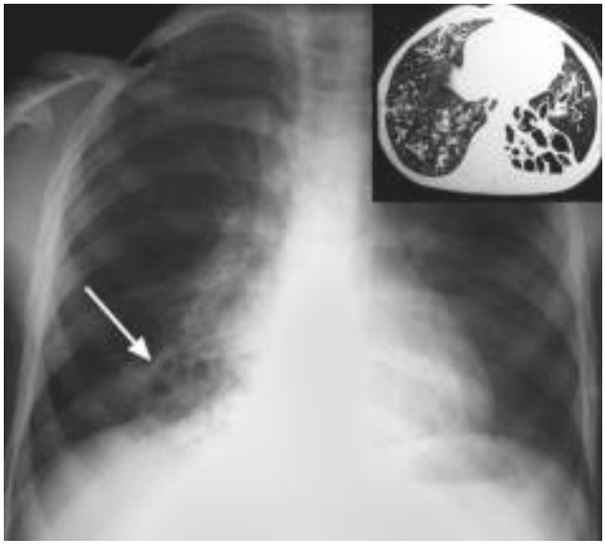


Fig. 16.12: **Bronchiectasis (right lower zone): Honey-comb appearance on X-ray chest and HRCT (Inset).**

AFB staining and culture of sputum, gastric lavage or brochoalveolar lavage is necessary to establish infective etiology.

- *Bronchoscopy* is indicated in selected cases to: (i) visualize and remove any obstructive cause, e.g. foreign body, (ii) collect bronchoalveolar aspirate for microbiology, and (iii) bronchial washing or toilet.
- Other relevant etiological investigations, e.g. tuberculin test, sweat chloride test, etc.

Management of bronchiectasis includes:

- *Effective clearance of mucus* by regular postural drainage, chest physiotherapy and bronchoscopy, if necessary. Airway hydration with inhaled hypertonic saline may improves quality of life in older children.
- *Elimination of infective foci* by systemic antibiotics, e.g. Coamoxclav during acute exacerbations for 2–3 weeks. Antibiotics should not be used indiscriminately and for prolonged duration, to avoid development of resistant infections. However, long-term prophylaxis with oral (macrolide) or nebulized antibiotics, (e.g. tobramycin, colistin, aztreonam) may be beneficial in selected cases.
- *Surgical resection of affected segment* is indicated in persistent localized bronchiectasis, while even lung transplant must be considered in severe bilateral disease.
- *Immunization* for common respiratory infections, e.g. influenza, pneumococci, etc. is recommended in all cases.

16.10.2 LUNG ABSCESS

Lung abscesses in children is usually due to: (a) *incomplete clearance of acute pneumonia,, though may also develop due to* (b) *aspiration of infected material* in debilitated children, (c) *bronchial obstruction* with poor mucus clearance, e.g. foreign body, tumors, sequestration etc., (d) *hematogenous spread* from distant septic foci, or (e) *direct spread* from surrounding tissues, e.g. amebic abscess from liver.

Post-aspiration abscesses are common in dependent parts, i.e. right lower lobe in older children and right apical region in infants/bed-ridden children.

Etiology: *Staph. aureus* and *Klebsiella* are two most common pathogens in lung abscess, though anaerobic infection from oral flora, e.g. bacteroides, fusobacterium, etc. are also common. Abscesses due *E. histolytica*, Actinomyces, Nocardia, etc. are rare in childhood. Staphylococcal abscesses are usually multiple, while those following aspirations are usually solitary.

Clinically, lung abscesses usually present with insidious onset of: (a) wet-cough with copious, purulent and foul-smelling expectoration, (b) persistent fever and constitutional signs, (c) clubbing and growth failure.

Common lung signs include localized dullness, bronchial (amphoric or cavernous) breathing and coarse crepitations.

Complications may be *local*, e.g. empyema, pneumothorax, bronchiectasis or bronchopneumonia or *distant*, i.e. metastatic abscesses in other tissues.

Diagnosis depends on: (a) X-ray chest, showing a cavity with/without fluid level **(Fig. 16.13)**, (b) CT chest, and (c) gram-staining/culture of sputum. USG/CT guided percutaneous drainage of abscess for staining and culture is indicated in non-responders.

Treatment: Empirical antibiotic therapy must include an anti-staphylococcal agent, e.g. cloxacillin or vancomycin, along with an antibiotic against anaerobes, e.g. clindamycin, Ticarcillin or metronidazole; for at least 3–6 weeks, which needs to be modified after culture reports.

Fig. 16.13: **Lung abscess.**

Percutaneous CT-guided or thoracoscopic drainage is indicated only in severely sick and non-responding cases or those with associated empyema. Gradual resolution of abscess must be demonstrated on serial skiagrams.

16.10.3 CYSTIC FIBROSIS

Cystic fibrosis (CF), the commonest cause of chronic lung disease and malabsorption syndrome in western countries, is rare in India though being increasing diagnosed in recent years on genetic testing.

Pathogenesis: CF is an autosomal recessive disorder of *cystic fibrosis transmembrane conductance regulator protein* (CFTR) gene on chromosome 7, with a pathognomonic defect in transport of salts (Na^+ and Cl^-) and water across secretary epithelia, leading to:

- Desiccation of respiratory mucus, causing airway obstruction and chronic lung disease
- Desiccation of pancreatic and biliary secretions, causing obstruction of respective ducts with malabsorption/biliary cirrhosis
- Desiccation of sweat, with increase in sweat Na^+ and Cl^- contents.
- Similar abnormalities in other exocrine ducts, e.g. vas deferens (azoospermia), etc.

Carriers with single pathogenic variant may be asymptomatic or occasionally develop a disease limited to one organ system, known as *CFTR-related disorder*.

Clinically, CF is a multisystemic disease though respiratory manifestations are predominant cause of morbidity and mortality with variable time course.

Meconium ileus is the earliest presentation in ~10–20% newborns leading to intestinal obstruction, though most cases present beyond neonatal period with:

- *Respiratory manifestations*, e.g. recurrent infections and wheeze in early infancy, followed by secondary complications, e.g. bronchiectasis or recurrent pneumothorax. Sinusitis and nasal polyps are common.
- *GIT manifestations*, e.g. malabsorption due to exocrine pancreatic insufficiency, with failure to thrive, steatorrhea, hypoproteinemia, etc. Intermittent abdominal pain and intestinal obstruction is common.
- *Skin manifestations*, e.g. salty frost or taste over the skin. Excessive loss of salts in sweat also leads to hyponatremia and dehydration, specially in hot weather or febrile children.
- *Late manifestations*, e.g. biliary cirrhosis, diabetes, delayed puberty or sterility/infertility may develop in surviving adolescents.

Diagnosis depends on following criteria (A and B both):

A. *Presence of at least one of the following:*
   - At least one phenotype with chronic pulmonary disease, chronic sinusitis, characteristic gastrointestinal and nutritional abnormalities, salt-loss syndromes or obstructive azoospermia;
   - History of CF in a sibling;
   - Positive newborn screening test.

B. *PLUS at least one of the following:*
   - Elevated sweat chloride concentration (>60 mEq/L):
   - Two *CFTR* gene mutations, known to cause CF on separate alleles:
   - Abnormalities in nasal potential difference (NPD) testing typical for CF-NPD, suggesting abnormalities in ion transport across the nasal epithelium

For ***Sweat chloride test***, minimum 50 mg of sweat is collected on a filter paper wrapped around the forearm or back, after stimulating sweat production by 3 mA current passed through pilocarpine (pilocarpine iontophoresis).

Prenatal diagnosis is possible with ~90% sensitivity, though neonatal screening in high-risk cases is more cost-effective for early diagnosis. It involves a spot-test to detect immunoreactive trypsinogen in cord-blood, though diagnosis must be further confirmed by sweat-chloride test or molecular studies.

Management aims to prevent/treat pulmonary complications and secondary infections as well as to maintain adequate nutrition, as follows:

- *Prevention of pulmonary complications* with:
  - Frequent nebulizations with hypertonic saline, to liquefy mucus followed by chest physiotherapy.
  - Prolonged antibiotic therapy, specially to cover Pseudomonas and staphylococci-predominant pathogens in CF. Aerosolized tobramycin or aztreonam therapy 2–3 times a day on alternate months has been recommended in cases with chronic *pseudomonas colonization* to reduce morbidity.
  - Treatment of acute exacerbations with oral or IV antibiotics, intensified airway clearance therapies, and respiratory support.
  - Endoscopic removal of airway obstruction, e.g. mucus with bronchopulmonary lavage. Intrabronchial antibiotics may also be instilled.
  - Early diagnosis and treatment of complications, e.g. collapse, pneumothorax, hemoptysis, etc.
  - Steroids, mucolytics and expectorants, though commonly used, are of limited value in CF.
- *Nutritional therapy* with adequate dietary support, pancreatic enzyme replacements, vitamin and mineral supplements, etc.
- *Fluid and electrolyte correction* in cases with significant salt depletion. *Hypochloremic alkalosis* is the commonest metabolic abnormality in CF.
- *Treatment of other complications*, e.g. meconium ileus, intestinal obstruction, pancreatitis, rectal prolapse, nasal polyps and liver disease, etc.

***CFTR modulator therapy* with** many drugs, e.g. Ivacaftor, Lumacaftor, Tezacaftor and Elexacaftor,

has been recently approved for use in selected cases depending on the age and genotype, to modulate *CFTR* gene functions, either alone or in combinations.

Prognosis: Untreated cases succumb in early childhood due to lung problems, though supportive therapy has improved life span in recent years.

16.10.4 INTERSTITIAL LUNG DISEASES

Interstitial lung diseases (ILD) also referred as *diffuse lung diseases (DLD)*, include a large group of uncommon, heterogeneous, familial or sporadic diseases of lung interstitium and distal air spaces that cause significant impairment of gas exchange. Some classification systems exclude DIDs with established etiology, e.g. cystic fibrosis, bronchopulmonary dysplasia, etc. and use the term ***child syndrome*** to denote rest of these disorders.

Etiology of ILDs is extremely heterogeneous. While developmental or genetic disorders of surfactant dysfunction are more important in infants, post-infectious, environmental or systemic causes dominate in older children **(Table 16.26)**.

Pathophysiology varies with the cause, with common feature of the remodeling of the distal airspaces, leading to impaired gas exchange. Earlier thought to be a sequel of persistent underlying inflammation, current paradigm has shifted from inflammation to the tissue injury with aberrant wound healing and collagenous fibrosis. Fibrotic remodelling of airways and alveoli leads to persistent hypoxemia that in turn results in vascular remodeling and pulmonary hypertension, i.e. *cor pulmonale*.

Clinical presentation varies with the cause, though most cases present with insidious onset of persistent (not episodic) respiratory distress which may gradually lead to persistent hypoxia, hypercarbia and failure to thrive. Chest examination is surprisingly near-normal despite the dyspnea. Appearance of persistent cyanosis with loud P_2 suggests development of cor pulmonale.

Diagnosis of ILD must be considered in after exclusion of common causes in cases with at least 3 of the following 4 criteria:

a. Persistent or progressive respiratory symptoms, e.g. cough, dyspnea and exercise intolerance;
b. Persistent or progressive respiratory signs, e.g. tachypnea, adventitious sounds, retractions, clubbing, failure to thrive or respiratory failure;
c. Persistent or progressive hypoxemia; and
d. Diffuse abnormalities on a chest X-ray or CT scan **(Fig. 16.14).**

Detailed history may help to identify the underlying cause, e.g. positive family history (surfactant dysfunction), exposure to molds/birds (hypersensitivity pneumonitis), hemoptysis (pulmonary hemosiderosis), rash or arthritis (connective tissue disease)

TABLE 16.26: Interstitial lung diseases in infants and young children (American Thoracic Society 2013)

Disorders most prevalent in infancy

- ***Diffuse developmental disorders:***
  - Acinar dysplasia,
  - Congenital alveolar dysplasia
  - Alveolar capillary dysplasia
- ***Growth abnormalities with deficient alveolarization:***
  - Pulmonary hypoplasia
  - Bronchopulmonary dysplasia
  - Chromosomal disorders, e.g. Down syndrome
  - Congenital heart disease
- ***Specific conditions of undefined etiology:***
  - Neuroendocrine cell hyperplasia of infancy
  - Pulmonary interstitial glycogenosis
- ***Surfactant dysfunction disorders:***
  - Pulmonary alveolar proteinosis (PAP)
  - Desquamative interstitial pneumonia (DIP)
  - Non-specific interstitial pneumonia (NsIP)
  - Chronic pneumonitis of infancy (CIP)

Disorders not-specific to infancy

- ***Disorders of normal host:***
  - *Post-infectious:* Adenovirus, Influenza, mycoplasma
  - *Environmental:* Hypersensitivity pneumonitis, toxic inhalation
  - *Others:* Recurrent aspiration, eosinophlic pneumonia
- ***Disorders related to systemic diseases:***
  - *Immunological:* SLE, Good-Pasture syndrome
  - *Storage disorders:* Gaucher disease
  - *Hematological:* Histiocytosis
  - *Others:* Sarcoidosis, hemosiderosis
- ***Disorders related to Immunodeficiency states:***
  - Lymphocytic Interstitial Pneumonitis (LIP) in HIV
  - Granulomatous lymphocytic ILD of CVID
  - *Opportunistic infections:* Chemotherapy, radiation, transplant
- ***Disorders masquerading as ILD:***
  - Pulmonary vasculopathies
  - Pulmonary lymphatic disorders
  - Congestive lung due to cardiac dysfunction
  - Unclassified

Chest X-rays may be normal in ILD despite severe clinical disease or may show interstitial, reticular, nodular, or honeycombed lesions **(Fig. 16.14)**. *HRCT chest* is more informative showing air trapping, ground-glass patterns, mosaic patterns of attenuation, hyperinflation, bronchiectasis, cysts, and/or nodular opacities. It also helps to select the site for lung biopsy and monitor the progression of disease.

Pulmonary function tests are useful to assess the severity of pulmonary dysfunction and response to treatment. Most cases reveal restrictive lung disease with decreased lung volumes and compliance. Diffusion capacity of the lung is often reduced. Exercise testing may detect pulmonary dysfunction even in the early stage of ILD with a decline in oxygen saturation.

Fig. 16.14: **Interstitial lung disease.**

Bronchoalveolar lavage may be useful to detect secondary infection, bleeding and aspiration, as well as to collect samples for cytology and molecular analyses.

Lung biopsy is often necessary for diagnosis. Genetic testing for surfactant dysfunction mutational analysis is indicated in infants and toddlers with ILD.

Management revolves around *supportive care* with supplemental oxygen for hypoxia, adequate nutrition for growth failure and antimicrobials for secondary infections. Some children may benefit symptomatically with bronchodilators.

Immunosuppressive therapy with systemic corticosteroids for 6–8 weeks is the treatment of choice in most cases of chILD, though controlled trials are lacking. Alternatives include other immunomodulators, e.g. hydroxychloroquine, azathioprine, cyclophosphamide, cyclosporine, methotrexate, intravenous immunoglobulin, etc. *Investigational approaches* involve specific agents directed against the action of cytokines, growth factors, or oxidants. *Lung transplant* for progressive or end-stage ILD has been successful in some cases.

Specific treatment is available for some DLDs including antimicrobials for certain infections, management of swallowing dysfunction and/or GERD in patients with chronic aspiration, avoidance of the offending antigen in hypersensitivity pneumonitis, and whole lung lavage for older children with pulmonary alveolar proteinosis.

Outcome of chILD is variable. Some children recover spontaneously without treatment, but others may progress to death. Reported 5-year mortality rates vary from ~30–50%. Pulmonary hypertension, failure to thrive, and severe fibrosis are considered as poor prognostic indicators.

Prevention includes avoidance of inhalation irritants, immunization for respiratory infections and genetic counseling in cases of positive familial history.

16.10.5 CONGENITAL LUNG MALFORMATIONS

Congenital lung malformations are rare but important causes of respiratory morbidity in children with outcome dependent on the size of lesion and secondary changes, e.g. infection or hemorrhage. Failure to recognize them may lead to inappropriate delay in appropriate management.

Pulmonary agenesis/aplasia denotes *complete absence of a lung*. Bronchial stump is also absent in agenesis but present in aplasia. Pulmonary agenesis may be autosomal recessive or associated with other malformations, e.g. *VACTERL sequence.*

Clinically, bilateral lung agenesis is incompatible with life, while unilateral defects may be asymptomatic due to compensatory growth of the remaining lung or present at any age with non-specific respiratory illness. Scoliosis is common in older children.

Chest skiagram shows unilateral lung or lobar collapse and diagnosis must be confirmed by CT/MRI. Other congenital anomalies must also be excluded.

Treatment is conservative, though surgery may benefit selected cases.

Pulmonary hypoplasia denotes *decrease in numbers of alveoli and airway generations*, usually due to intrauterine pressure that prevents normal lung development, e.g. diaphragmatic hernia or oligohydramnios. Depending on the severity, pulmonary hypoplasia may present in newborns with respiratory insufficiency or persistent pulmonary hypertension *or* at a later age with recurrent respiratory illnesses. Diagnosis requires lung imaging studies, preferably MRI. Treatment depends on the severity and some cases may need mechanical ventilation, treatment of pulmonary hypertension or extracorporeal membrane oxygenation to sustain life.

Congenital cystic adenomatous malformation (CCAM) or congenital pulmonary airway malformation (CPAM) is the *presence of hamartomatous cystic lung tissue mixed with normal lung* due to mal-development of terminal bronchiolar structures in early gestation. Among the five histologic types, commonest is type I disease (60%) with single or multiple large cysts involving only a part of one lung.

Clinically, most cases present in early infancy with respiratory distress, recurrent respiratory infections and pneumothorax, often confused with a diaphragmatic hernia or lung abscess.

Diagnosis rests on CT scan **(Fig. 16.15)**, and prenatal diagnosis is possible on ultrasonography. Treatment is surgical, though may be delayed in asymptomatic cases

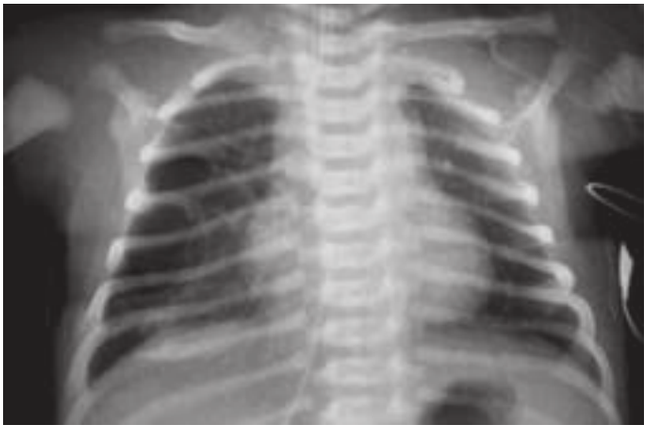


Fig. 16.15: **Congenital cystic adenomatous malformation.**

till one year of age due to rare possibility of spontaneous resolution. Malignant changes are possible in unoperated cases.

Antenatal intervention is controversial as many prenatally detected cysts regress in size postnatally.

Pulmonary sequestration is a congenital anomaly of lung development in which a part of the lung tissue does not connect to a bronchus and receives its blood supply from the systemic arteries. Sequestration may be *intrapulmonary* (more common) or *extrapulmonary*, depending on the location. Associated anomalies, e.g. CCAM and diaphragmatic hernia are not uncommon.

Clinically, sequestration functions as a space occupying lesion in the chest and most cases are asymptomatic. Some cases present with secondary infection, abscess or hemoptysis.

Diagnosis is confirmed by CT chest and contrast studies are necessary to assess vascular supply before surgery.

Treatment is surgical though coil embolization of feeding artery may be successful in selected cases.

Bronchogenic cysts denote *abnormal budding of the tracheal diverticulum of the foregut*, more common on the right, near midline. Rarely demonstrable at birth, these cysts usually present later after secondary infection and enlargement. Large cyst may also compress adjacent airway.

Chest skiagram usually shows solid coin lesions or air-filled cyst with/without fluid level **(Fig. 16.16)**, though diagnosis must be confirmed on CT/MRI before surgery.

Treatment is surgical excision after appropriate antibiotics. Excision is advised even for asymptomatic cysts due to risk of future infection.

16.11 MISCELLANEOUS LUNG DISORDERS

This chapter deals with some common acute or chronic lung disorders, not discussed elsewhere.

Fig. 16.16: **Bronchogenic cyst.**

Atelectasis (collapse) denotes *impaired expansion of alveoli with loss of lung volume*, either due to absorption of alveolar air after airway obstruction or compression of alveoli by external pressure.

Etiologically, collapse may classified as:

- *Obstructive collapse*, due to intra-bronchial obstruction by foreign body, caseous material or mucus plugs, etc. or extra-bronchial obstruction by lymph node, tumors, etc.
- *Pressure collapse,* due to compression of lung parenchyma, e.g. in plural effusion, pneumothorax, diaphragmatic hernia, tumors, etc. Pressure collapse may also develop due to deformities of thoracic cage/spine.

Reduced surfactant production in preterm newborns is another cause of atelectsis in newborns or in some inhalant poisonings.

Clinical manifestations depend on the cause, severity and duration of collapse. While sudden collapse in previously normal lung may present with significant respiratory distress, long-standing collapse may be entirely asymptomatic.

Characteristic clinical signs include-(a) shift of trachea/mediastinum towards affected side, (b) dull percussion note, and (c) diminished air entry/vocal resonance. However, bronchial breathing with increased vocal resonance is common, if collapsed lung overlies a patent bronchus.

Diagnosis generally rests on *chest skiagrams*, showing: (a) tracheal shift on same side with overcrowding of ribs, and (b) homogeneous patchy or segmental opacity, with sharp and contracted borders **(Fig. 16.17)**.

Right lower lobe collapse is most likely due to foreign body, while right middle lobe collapse is usually tubercular in origin following bronchial compression by mediastinal lymph nodes (*middle lobe syndrome*).

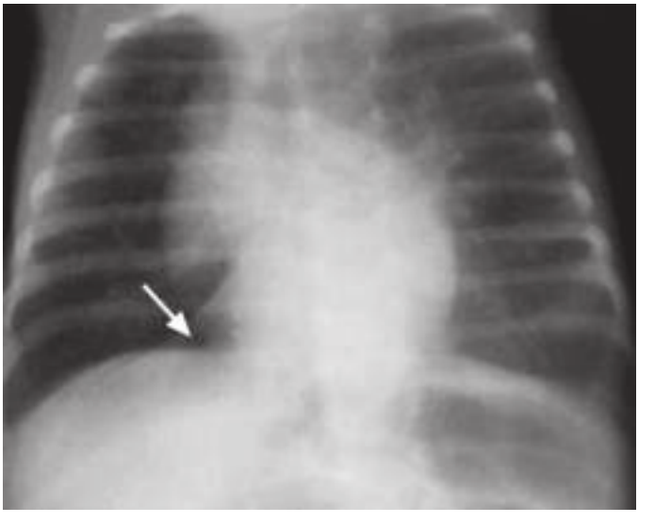


Fig. 16.17: **Collapse of the lower zone in right lung.**

Bronchoscopy is essential in all cases of persistent collapse with unknown etiology or suspected foreign body.

Management includes: (a) bronchoscopic removal of obstructing material, e.g. foreign body or mucus plugs, (b) chest physiotherapy with postural drainage and breathing exercises, (c) treatment of primary cause.

Persistent collapse for >4–6 weeks is unlikely to be reversible and becomes a nidus for chronic infection or bronchiectasis. Surgical resection, i.e. lobectomy or pneumonectomy, may be necessary in these cases to prevent development of bronchiectasis and further spread of infection.

Emphysema, i.e. *distension of air spaces with irreversible disruption of alveolar septa* may be localized or generalized. Mere distension of alveoli, without septal disruption, is called *overinflation.*

Etiology: Common causes of emphysema include:

- *Partial airway obstruction* (ball-valve mechanism) with expiratory air trapping by foreign body, mucus plugs or endobronchial tuberculosis.
- *Compensatory emphysema,* to overtake the function of diseased or surgically removed lung.
- *Congenital lobar emphysema (CLE),* either primary or due to secondary to bronchomalacia, bronchial stenosis/mucosal folds or aberrant vessels.
- *Generalized air trapping and emphysema* in asthma, cystic fibrosis, 1-antitypsin deficiency and interstitial lung diseases. Unilateral hyperlucency of lung following infections is termed as *Swyer-James syndrome*.

Clinically, emphysema is rarely symptomatic, except CLE that may present with respiratory distress in newborns or early infancy. Generalized emphysema may be associated with overinflation of chest and resonant percussion note.

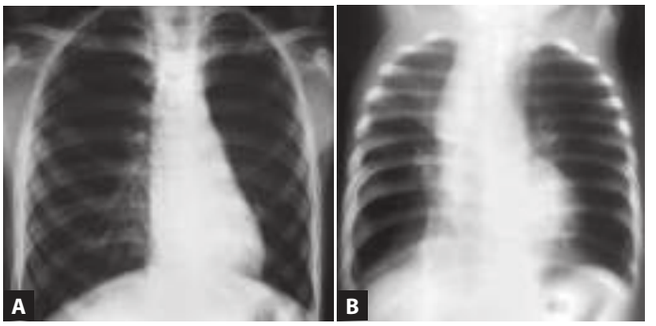


Fig. 16.18: **Emphysema: (A) Bilateral; (B) Segmental (Right lower zone)**

Diagnosis rests on chest X-ray showing *localized or diffuse hyperlucency* **(Fig. 16.18)** but with visible bronchovesicular markings and no mediastinal shift (d/d pneumothorax).

Treatment depends on primary cause. Congenital lobar emphysema may be associated with herniation of the lung across the mediastinum and needs lobectomy to prevent compression of other parts.

Pulmonary edema denotes transudation or exudation of fluid from interstitial capillaries to alveolar space due to:

- Increased pulmonary vascular pressure, e.g. heart disease, left ventricular failure, etc.;
- Increased pulmonary blood volume, e.g. overhydration, renal failure;
- Decreased plasma oncotic pressure, e.g. nephritic syndrome, hypoproteinemia;
- Altered capillary permeability due to alveolar inflammation, e.g. acute respiratory distress syndrome (ARDS), etc.
- *High altitude* pulmonary edema, due to low atmospheric pressure.

Clinically, it presents with progressive dyspnea, wheezing and cough with *frothy, pinkish expectoration.*

Bilateral coarse, bubbly crepitations are common, specially in basal region.

Diagnosis rests on chest skiagram showing bilateral generalized haziness of lungs with/without *Kerley's lines,* i.e. linear streaks extending from hilum to periphery due to dilated lymphatics.

Presence of cardiomegaly, perihilar butterfly distribution of edema and Kerley's lines indicate cardiogenic pulmonary edema while normal heart size with peripheral/patchy distribution of edema and presence of air bronchogram suggests non-cardiogenic etiology **(Fig. 16.19)**.

Treatment is directed to primary cause with diuretics, cardiotonic drugs, e.g. digoxin, and bronchodilators along with oxygen/ventilatory support.

Pulmonary hypertension (PHT) may be—(a) *primary* or idiopathic, (b) *secondary to lung disease* or airway

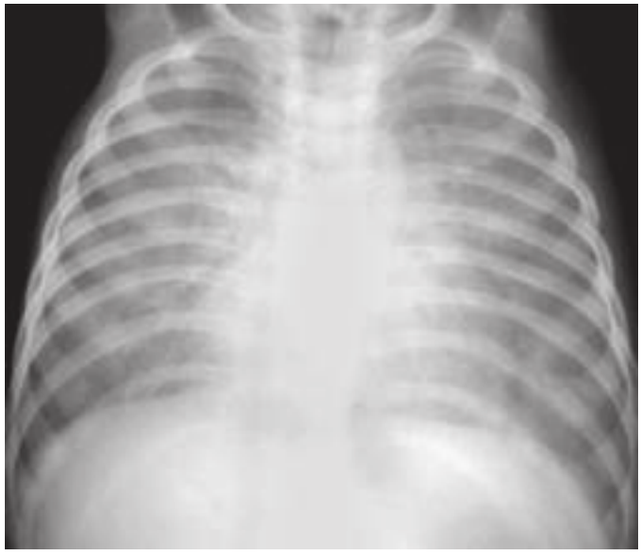


Fig. 16.19: **Pulmonary edema (ARDS).**

Fig. 16.20: **Empyema thoracis.**

obstruction, e.g. adenoids, pulmonary embolism, or (c) *secondary to cardiac disease* (Lt>Rt shunt). PHT due to lung disease may lead to right ventricular hypertrophy/dilation (*Cor pulmonale*) with congestive cardiac failure.

Diagnosis rests on cardiac evaluation (loud P_2) and confirmed on echocardiography and cardiac catheterization. Treatment is same as for CCF, though IV prostacyclines may help to reduce PHT in severe cases.

Persistent pulmonary hypertension in newborn (PPHN) is an important hemodynamic complication in sick newborns, discussed elsewhere (Ch 12.12.2) due to pulmonary vasospasm or hyperplasia leading to pulmonary hypertension and consequent right to left shunting through foramen ovale or PDA.

16.12 PLEURAL DISORDERS

Pleural disorders may be broadly divided into three categories: (a) *dry pleurisy*, i.e. pleural inflammation without significant fluid collection, (b) *pleural effusion*, i.e. collection of fluid into pleural space, and (c) *pneumothorax*, i.e. entry of air into pleural space.

Pleural effusions, depending on the type of fluid, are also referred as: (a) *empyema* thoracis (pus), (b) *exudative* pleural effusion (inflammatory but not purulent fluid), (c) *hydrothorax* (non-inflammatory transudative fluid), (d) *hemothorax* (blood), and (e) *chylothorax* (lymph), etc.

The term *parapneumonic effusion* is used to refer pleural effusion associated with underlying lung infection, e.g. pneumonia of any etiology.

16.12.1 EMPYEMA THORACIS

Empyema thoracis (pyothorax) is the commonest pleural disease in Indian children, though tubercular pleural effusion is more common in older children >5 years of age.

Etiology: Empyema thoracis is mainly caused by *Staph. aureus, H. influenzae,* and *S. pneumoniae.*

Most cases begin as *parapeumonic effusions* with underlying lung pathology, followed by secondary bacterial infection. However, infection may also reach pleural space directly by: (a) rupture of the lung abscess, (b) external trauma or thoracocentesis, (c) extension from abdomen, e.g. amoebic abscess and (e) extension from mediastinum, e.g. mediastinitis.

Pathologically, empyema generally evolves through three phases, i.e. thin and sterile *exudative phase* (1–3 days), *fibrinopurulent phase* (4–14 days) and *organization phase* (>14 days) with development of adhesions and septations.

Clinically, empyema presents with high fever, cough, breathlessness, chest pain and following findings-(a) shift of mediastinum on opposite side, (b) restriction of movements on affected side, (c) stony dull percussion note, (d) diminished breath sounds and (e) decreased vocal resonance/vocal fremitus. Bronchial breathing with increased vocal resonance may be present at the upper level of effusion.

Diagnosis is established on:

- *Chest skiagram* showing dense homogenous opacity with—(i) shift of mediastinum on opposite side, and (ii) obliteration of costophrenic/cardiophrenic angles **(Fig. 16.20)**. Upper border of fluid is usually curved due to surface tension, though typical findings may not be seen in loculated empyma.
- *USG* is the preferred investigations in all cases to confirm presence of fluid as well as for guided thoracocentesis/chest-tube insertion.
- *CT* scan is not routinely indicated, except to detect underlying abscess and before surgical interventions.

TABLE 16.27: D/D Pleural fluid findings

	Transudate	*Tubercular*	*Empyma*
Appearance	Clear	Straw	Turbid
Proteins (gm/dl)	<3	>3	>3
Sugar (gm/dl)	>60	<40	<40
Cells (predominant)	Nil	Lymphocytes	Polymorphs
LDH (IU/L)	<200	>200	>200

- *Pleural fluid examination*, with smear and culture is necessary to identify causative pathogen, while antigen-based or PCR-based tests are useful in culture negative or pre-treated cases.

Clinical and radiological signs are generally similar in all pleural effusions and etiological differentiation is possible only on pleural fluid examination **(Table 16.27)**.

Complications: Untreated empyema may progress to cause: (a) pyopneumothorax, (b) bronchopleural fistula, (c) *empyema necessitans* (rupture into thoracic wall) or (d) thick pleural adhesions, leading to restrictive lung disease.

Management depends on the stage of disease, type of the fluid, presence of septations/membranes and response to therapy **(Table 16.28)** and includes:

- ***Removal of fluid*** by thoracocentesis or closed intercostals drainage (ICD). While maximum pleural fluid should be removed at the time of diagnostic tapping, ICD is necessary in almost all cases with significant empyema. Tube should be kept *in situ* until the drainage is <30–50 ml/day or cavity size is <50 ml. Deep breathing exercises and incentive spirometry help in better ICD drainage.

  Some workers recommend intrapleural instillation of fibrinolytic agents, e.g. streptokinase (10,000–20,000 U/kg in 50 ml Normal saline) or Urokinase (10,000–40,000 IU in 10–40 ml of normal saline) every 12 hrs for 6 doses, in cases with multi-loculated empyema.
- ***Antibiotic therapy***, based on *in vitro* sensitivity of cultured organism. For empirical therapy, a third generation cephalosporin (IV Cefotaxime or Ceftriaxone) *with cloxacillin or v*ancomycin, for minimum 3–4 weeks is preferable. Therapy should be modified after culture reports. Intrapleural instillation of antibiotics is no longer recommended.
- ***Surgical decortication*** via video assisted thoracoscopic surgery (VATS) or open thoracotomy is needed in cases with no response after 72 hours of ICD and specific antibiotics.

Other important types of pleural effusions include:

Dry (plastic) pleurisy, without significant effusion is usually seen in early empyema, viral infections, sub-pleural tubercular lesions and connective tissue disorders.

TABLE 16.28: Management of empyema thoracic

Stage	*Management*
I. Exudative *(Clear free-flowing fluid)*	Antibiotics ± ICD (if no improvement)
II. Fibrinopurulent *(Septations/ loculations)*	Antibiotics + ICD + fibrinolytics/ VATS
III. Stage III (organized) *(Solid fibrous peel/membrane)*	VATS/Mini-thoracotomy

ICD: Intercostal drainage; **VATS:** Video-assisted thoracoscopic surgery

Clinically, these cases presents with characteristic *chest pain* due to friction between two inflamed layers of pleura, which aggravates on coughing or deep inspiration and *pleural rub*, without signs of significant pleural effusion.

Diagnosis depends on chest skiagram, showing diffuse haziness or sharply demarcated homogenous opacity. Mediastinal shift is unlikely, considering small size of effusion.

Treatment is mainly directed towards the primary cause, though chest strapping may help to relieve the pain.

Exudative pleural effusion: Tuberculosis is the leading cause of non-purulent exudative pleural effusion (*serofibrinous pleurisy*), followed by pneumococcal or streptococcal pneumonia, collagen disorders, e.g. SLE, and intrathoracic malignancies.

Clinical presentation depends on the amount of fluid. Pleuritic pain and rub may be present in early stages but disappear soon after the collection is large enough to separate two layers of pleura. Apart from features of primary disease, signs of exudative pleural effusions are similar to empyema thoracis.

Diagnosis rests on—(a) chest skiagram, (b) USG, and (c) pleural fluid examination. Microbiological and serological studies in pleural aspirate, with special reference to tuberculosis and connective tissue disorders, are necessary to confirm etiology.

Management includes—(a) treatment of primary cause, and (b) therapeutic thoracocentesis, only in cases with large effusions causing respiratory distress. However, rapid removal of more than one litre of fluid may lead to re-expansion pulmonary edema and must be strictly avoided. Intercostal drainage may be needed if fluid refills rapidly or there is possibility of bacterial infections. However, it should be avoided in tubercular effusions, due to risk of fistula formation.

Hydrothorax, i.e. collection of non-inflammatory (transudative) fluid in pleural space, is caused by: (a) *decreased oncotic pressure* in hypoproteinemic states, e.g. nephritic syndrome, kwashiorkor; and (b) *increased hydrostatic pressure* in pleural vasculature, e.g. CCF, superior vena caval compression syndrome.

Clinical presentation depends on primary cause and lung signs are similar to other pleural effusions. Ascites and edema is common in hypoproteinemic states.

Diagnosis rests on thoracocentesis to reveal transudative pleural fluid **(Table 16.27)**.

Management is directed towards primary cause and therapeutic pleural tap is rarely indicated, except in cases with respiratory distress due to large fluid accumulation.

Hemothorax, i.e. bleeding in pleural space, is rare in childhood, caused by—(a) thoracic trauma. (b) intrathoracic neoplasms, (c) systemic bleeding disorders, (d) post-thoracic surgery, and rarely, (e) congenital vascular anomalies of pleura/lung.

Diagnosis is established on thoracocentesis and hemorrhagic pleural fluid should always be examined for malignant cells.

Management includes treatment of primary cause, blood transfusions, intercostal drainage to prevent organization of blood and surgical intervention to treat the site of bleed, if identifiable.

Chylothorax, i.e. collection of lymph or chyle in pleural space, is caused by thoracic duct obstruction or injury due to—(a) cardiothoracic surgery, (b) thoracic trauma, (c) intrathoracic malignancy, and (d) congenital anomalies of thoracic duct (in newborns). Chylothorax is more common on left side, rarely being bilateral in severe cases.

Diagnosis rests on pleural tap that reveals a milky-white fluid due to high fat content, although it may be clear in newborns before feeds are given.

Presence of chyle may be confirmed by a simple *bedside test,* i.e. mixing of pleural fluid with ether, formaldehyde or any alkali, which clears the haziness of fluid. Triglyceride levels are high in chylous effusion.

Management: Spontaneous recovery occurs in >50% cases though repeated pleural aspirations may be needed to relieve intrathoracic pressure. Low-fat diet with medium chain triglycerides is advisable till spontaneous recovery. Total parenteral nutrition and surgical ligation of thoracic duct may be required in difficult cases.

16.12.2 PNEUMOTHORAX

Pneumothorax denotes accumulation of air within the pleural space, usually due to air-leak from underlying lung. It may also be associated with pus (pyopneumothorax) or fluids (hydropneumothorax).

Etiology: Pneumothorax may be idiopathic (spontaneous) or secondary to underlying lung disease. Staphylococcal pneumonia, congenital/acquired emphysema and iatrogenic injury due to forced mechanical ventilation are three leading causes of pneumothorax in children **(Table 16.29)**.

Recurrent pneumothorax is seen in cases with: (a) underlying congenital cyst/bullae, (b) cystic fibrosis, and (c) collagen defects, e.g. Marfan syndrome or Ehlers-Danlos syndrome with inherently weak pleura.

TABLE 16.29: Causes of pneumothorax

- **Air-leak from the lungs**
  - Pneumatoceles (*Staph. pneumonia*)
  - Emphysematous bullae (asthma, foreign body)
  - Congenital lung cysts or lobar emphysema*
  - Cavitatory tuberculosis
  - Cystic fibrosis*, α_1 antitrypsin deficiency*
  - Weak pleura* (Ehlers-Danlos syndrome)
  - Iatrogenic (Forced mechanical ventilation)
- **Air entry from external communication**
  - Trauma (penetrating thoracic injury)
  - Iatrogenic (thoracocentesis/surgery)
- **Spontaneous pneumotorax (idiopathic)**

*Causes of recurrent pneumothorax.

Clinical manifestations depend on the amount of air collected in pleural space and generally include:

- Sudden onset or exacerbation of respiratory distress,
- Local signs—(i) bulging of chest wall on affected side, (ii) shift of mediastinum on opposite side, (iii) tympanic note on percussion, and (iv) diminished breath sounds.
- Development of severe circulatory compromise/shock indicates *tension pneumothorax* due to marked increase in intra-pleural pressure following continuous air-leak, e.g. in bronchopleural fistula.

Diagnosis of pneumothorax should always be suspected in children with pneumonia or ventilator therapy, who develop sudden unexplained increase in respiratory distress.

Confirmation requires *chest skiagram* showing: (a) extreme hyperlucency with absence of lung markings, (b) underlying collapsed lung with well-defined margins, and (c) shift of mediastinum on opposite side with widening of rib spaces **(Fig. 16.21)**. Air-fluid interface with horizontally straight level indicates hydropneumothorax **(Fig. 16.22)**.

Fig. 16.21: **Pneumothorax (left side).**

Fig. 16.22: **Hydropneumothorax (right side).**

In emergency, diagnosis may be confirmed by insertion of a 21-gauze needle in 2nd intercostal space, connected to an underwater seal. Passage of air bubbles in water indicates pneumothorax.

D/D includes other causes of radiological hyperlucency, e.g. emphysema, large air-filled cavity or cysts, and diaphragmatic hernia.

Management depends on underlying cause and severity of pneumothorax and includes:

A. Removal of pleural air may be life-saving in large pneumothorax, though not necessary in all cases. General guidelines are as follows:

- *Mild or even moderate size pneumothorax in an otherwise normal child, occupying <30% of hemithorax* usually recovers spontaneously within a week. Administering 100% oxygen may hasten resolution.
- *Moderate to severe pneumothorax* need intercostals drainage of air (*closed thoracotomy)* from 2–3rd intercostal space, till the expansion of underlying lung. Two separate tubes in higher and lower intercostal spaces may be needed to drain air and pus respectively, in pyopneumothorax. Emergency needle-aspiration may be life saving in tension pneumothorax.
- *Persistent or recurrent pneumothorax* requires obliteration of pleural space by:
  - *Chemical pleurodesis*, i.e. instillation of an sclerosing agent, e.g. *talc*, in pleural space to cause inflammatory adhesion of pleural layers, or
  - *Open/thoracoscopic thoracotomy* with closure of bronchopleural fistula and stripping of pleura.

B. Supportive therapy includes:

- Oxygen supplementation with 100% oxygen to relieve respiratory distress and hasten absorption of air by increasing the nitrogen pressure gradient between pleura and blood.
- Treatment of primary disease, (e.g. antibiotics) and
- Symptomatic therapy for fever, pleuritic pain, etc.

Pneumomediastinum, i.e. *presence of air in mediastinal space*, is usually caused by rupture of alveoli in lung diseases, e.g. pneumonia or asthma: Leaked air dissects through perivascular sheaths to move toward hilum and enter the mediastinum. Air may also enter from non-pulmonary sources, e.g. esophagus following intractable vomiting, corrosive esophageal injuries/foreign bodies and chest wall trauma.

Clinical diagnosis is difficult but may be suggested by the presence of subcutaneous emphysema, obliteration of cardiac dullness or mediastinal "crunch" (*Hamman sign*). Final diagnosis rests on chest skiagram showing presence of air in the mediastinum.

Treatment is directed to the underlying disease and most cases resolve spontaneously. Tracheostomy or percutaneous drainage is very rarely needed to decompress the mediastinal space.

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CHAPTER 17

Disorders of Cardiovascular System

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Cardiovascular problems in childhood are quite different than those in adults. Unlike dominance of coronary heart disease and essential hypertension in adults, congenital heart diseases (CHDs) contribute over 3/4th of cardiac disorders in children, followed by rheumatic heart disease (RHD) in adolescents. Hypertension in childhood is usually secondary to renal, vascular or endocrinal disease.

17.1 DEVELOPMENTAL CARDIOLOGY

Important developmental aspects of cardiovascular physiology may be broadly divided into four components: (a) Development of the heart, (b) Fetal circulation, (c) Adoptive circulatory changes at birth and (d) Adult circulation.

17.1.1 DEVELOPMENT OF HEART

Development of fetal heart **(Fig. 17.1)** begins from mesoderm in 3rd week of intrauterine life with:

- ***Formation of the cardiac tube*** (18–22 days) on ventral surface of embryo by angiogenic cell clusters with multiple folding and differentiation,
- ***Cardiac looping*** (22–24 days), i.e. bending of the cardiac tube ventrally and towards the right (*d-loop*) to bring future left ventricle on left side in continuation of sinus venosus and future right ventricle rightwards in continuation of truncus arteriosus. Abnormal bending at this stage leads to cardiac malpositions, e.g. dextrocardia (*L-loop*). Cardiac tube also starts contracting by this time, resembling mature cardiac rhythmicity.
- ***Morphological segmentation*** (24–28 days), i.e. appearance of internal horizontal bulges within the primitive cardiac tube to form four chambers: (i) *Common atrium* in continuation of sinus venosus, (ii) *Primitive ventricle,* connected to common atria by common atrioventricular canal, (iii) *Bulbous cordis*, connected to primitive ventricle by bulboventricular foramen, and (iv) *Truncus areteriosus*.
- ***Formation of mature heart*** (26–30 days) as follows:
  - *Common atrium* divides vertically in left atrium (LA) and right atrium (RA) by two incomplete septa-left-sided *septum primum* and right-sided *osteum secundum*, with a left-over communication via *foramen ovale*.
  - *Common atrioventricular canal* divides horizontally by fusion of endocardial cushions to produce atrioventricular septum and atrioventricular valves, i.e. mitral valve (MV) and tricuspid valve (TV).

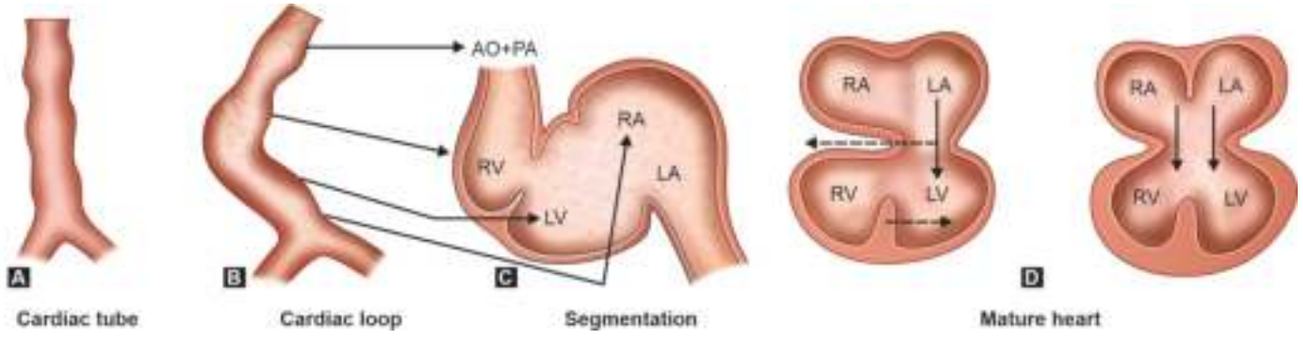


Fig. 17.1: Development of the heart.

TA: Truncus arteriosus; **BC:** Bulbous cordis; **PV:** Primitive ventricle; **CA:** Common atria; **RV:** Right ventricle; **LV:** Left ventricle; **RA:** Right atrium; **LA:** Left atrium; **AO:** Aorta; **PA:** Pulmonary artery.

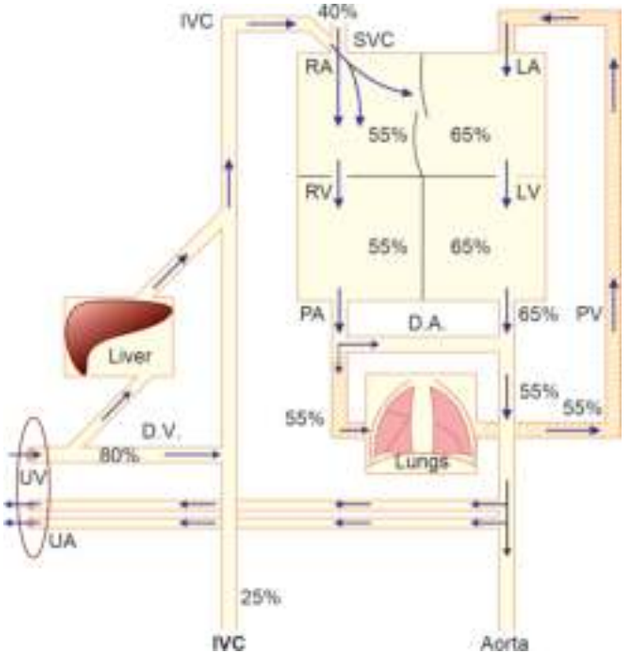
- *Primitive ventricle* develops into left ventricle (LV), while *bulbus cordis* develops into right ventricle (RV).
- *Bulboventricular foramen* elongates with septation to form interventricular septum.
- *Truncus arteriosus* divides length-wise to form ascending aorta connected with LV and pulmonary trunk connected to RV.

Remaining aorta, head and neck vessels and proximal pulmonary vessels develop from elongation of embryonic aortic sac and multiple arterial arches developing from it.

17.1.2 FETAL CIRCULATION

In utero circulation is maintained via placenta, with oxygenated blood from mother entering the fetal circulation via *single* umbilical vein and unoxygenated blood leaving via *two* umbilical arteries. Normal sequence of fetal circulation **(Fig. 17.2)** is as follows:

- Oxygenated blood (PaO_2 30–35 mm Hg) enters the fetus from placenta *via* single umbilical vein.
- Nearly half of this flow passes via portal vein to hepatic circulation and then to inferior vena cava (IVC), while the rest enters the IVC directly via ***Ductus venosus***. Ultimately all placental flow mixes with less oxygenated blood from lower extremities.
- IVC returns this mixed blood (PaO_2 26–28 mm Hg) to RA, where another less-oxygenated flow (PaO_2 18–22 mm Hg) also streams in via superior vena cava (SVC). However, mixing of these two flows is minimal at atrial level, as IVC flow is preferentially directed towards ***Foramen ovale*** to enter LA, while SVC flow mainly goes to RV via tricuspid valve.
- LA blood (PaO_2 26–28 mm Hg) passes to LV and then to aorta to supply head and neck vessels, before its mixing with RV outflow via ***Ductus arteriosus***.
- RV flow (PaO_2 18–22 mm Hg) enters pulmonary artery. However, due to high pulmonary resistance of unexpanded lungs, only ~10% of this flow enters pulmonary circulation. Remaining 90% of RV output is shunted through *ductus arteriosus* (Rt > Lt shunt) into aorta, bypassing the lungs.
- Mixing of less oxygenated RV flow with LV output drops the PaO_2 in distal aorta beyond the ductus arteriosus. Thus, *cerebral and coronary circulation in fetus is supplied by more-oxygenated pre-ductal flow, while other organs receive less-oxygenated post-ductal blood supply.*
- Nearly 60% of flow in descending aorta goes back to placenta via two umbilical arteries, for recycling.



(%) indicate percentage oxygen saturation of blood

Fig. 17.2: Hemodynamics: Fetal circulation.
UV: Umbilical vein; **DV:** Ductus venosus; **IVC:** Inferior vena cava; **SVC:** Superior vena cava; **PA:** Pulmonary artery; **DA:** Ductus arteriosus; **PV:** Pulmonary vein; **UA:** Umbilical artery.

In brief, fetal circulation is markedly different from postnatal circulation, on following points:

- *It is primarily dependent on umbilical flow* with all gaseous/metabolic exchange through placenta rather than the unaerated fetal lungs.
- *Systemic circulation runs parallel to pulmonary flow, rather than serially as in postnatal life,* with mixing at three levels — ductus venosus (umbilical artery > IVC), foramen ovale (RA > LA), ductus arteriosus (pulmonary artery > aorta). Actual pulmonary flow is negligible.
- *These mixing sites are vital to maintain parallel flow in fetal life* though none of them serves any physiological purpose after birth and get *obliterated* in early neonatal period.
- Due to high pulmonary resistance, *RV is the dominant ventricle in fetus,* unlike LV in adults.

17.1.3 FETAL TO NEONATAL TRANSITION

First breath after birth is a watershed event, when circulation changes from fetal to postnatal physiology. Two critical events at birth—sudden cessation of umbilical flow and expansion of lungs with first breath, trigger many hemodynamic changes to adopt from fetal to postnatal physiology, as follows:

- *Sudden drop in pulmonary vascular resistance* due to expansion of lungs and vasodilatory effects of increasing PaO_2.
- *Sudden rise in systemic vascular resistance* due to clamping of umbilical cord and obliteration of low resistance placental circulation.
- *Closure of ductus arteriosus* following equalization of pressures between pulmonary artery and aorta (due to *a* and *b* above). Rising PaO_2 of shunted blood

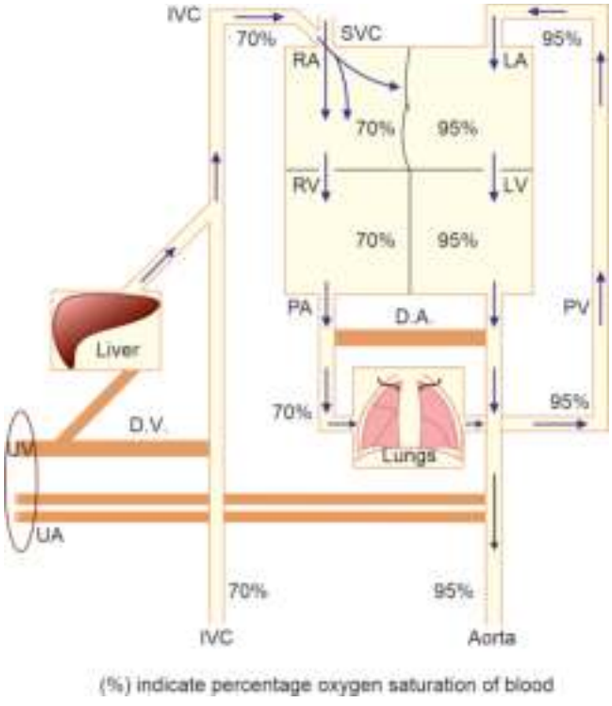


Fig. 17.3: Hemodynamics: Adult circulation.
For abbreviations see Fig. 17.2.

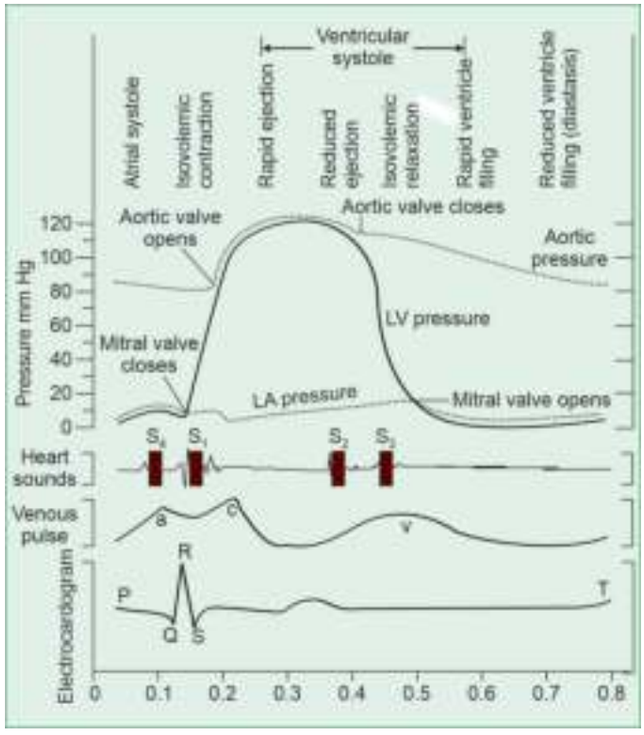


Fig. 17.4: Cardiac cycle.

through ductus arteriosus after lung expansion also contributes to its closure. While *functional closure of ductus is complete within 10–12 hours of birth, anatomical obliteration (ligamentum arteriosum) may take 4–6 weeks*.

- *Closure of foramen ovale* due to loss of pressure gradient between two atria *by*—(a) drop in RA pressure after 'opened-up' pulmonary circulation and reduced systemic venous return after cord clamping, and (b) rise in LA pressure due to increasing pulmonary venous return. While *functional closure of foramen ovale is complete within 4–6 hours of birth, anatomical closure takes many months or it may remain probe-patent throughout life.*
- *Closure of ductus venosus* by 7th day of life, changing into *Ligamentum venosum*.

Above mentioned changes transform the *'parallel'* fetal circulation into *'serial'* postnatal circulation at birth **(Fig. 17.3)**. Over the next few weeks, pulmonary vascular resistance continues to decline, leading to gradual shift from RV dominance in fetus to LV dominance in later life, with consequent changes in cardiac position, chamber pressures and axis.

17.1.4 POSTNATAL CIRCULATION

Postnatal circulation is mainly dependent on rhythmic contractility of the heart (cardiac cycle) and various pressure/resistance gradients between cardiac chambers and peripheral circulation.

Cardiac cycle: Each rhythmic contraction of the heart completes a set of changes in cardiac physiology, termed as *cardiac cycle*. In adults, each cycle lasts for ~0.8 seconds, including a smaller phase of ventricular systole (~0.3 second) and longer phase of ventricular diastole (~0.5 second). Atrial systole is limited to a smaller fraction of ventricular diastolic period (~0.1 second). During the remaining phase of cardiac cycle, atria remain in diastolic state to accept the venous return from systemic/pulmonary circulation.

A temporal sequence of various events in cardiac cycle is as follows **(Fig. 17.4)**:

- Onset of atrial systole by generation of electrical impulse from sinoatrial (SA) node, with rapid filling of ventricles,
- Closure of atrioventricular mitral and tricuspid valves, producing first heart sound,
- Isovolemic contraction of ventricles,
- Opening of semilunar aortic and pulmonary valves,
- Rapid ejection of blood from ventricles due to forceful ventricular systole (early systole),
- Slower ejection of blood from ventricles as the pressure gradient between ventricles and great vessels nears equalization and active ventricular contraction ends (late systole),
- Closure of semilunar valves, producing second heart sound,
- Isovolemic relaxation of ventricles,
- Opening of atrioventricular valves,

- Rapid filling of ventricles due to atrioventricular pressure gradient (early diastole),
- Slower filling of ventricles due to reducing atrioventricular pressure gradient (late diastole),
- Onset of atrial systole to restart the cycle.

Pressure and resistance relationships: Pressures in various cardiac chambers and circulation circuits depend on the amount of blood flow and resistance offered by forward flow. Note that:

- Amount of blood flow in systemic and pulmonary circulation is equal in normal children,
- As the systemic circulation provides more resistance to blood flow than the pulmonary circulation, LV pressure is much higher (120/0–10 mm Hg) than in the RV (25/0–6 mm Hg). LV pressure is also higher due to more muscle mass than the RV. *Hence, whenever there is an artificial communication between two sides,* e.g. *VSD or PDA, shunt is from left to right side,* unless other abnormalities are present.
- As both atria have negligible muscle mass, atrial pressures are much lower than ventricular pressures and nearly comparable on both sides (0–6 mm Hg in RA and 6–10 mm Hg in LA). *Hence, there is no significant shunting in ASD.*

Relative pressures/resistance gradients between various points in systemic and pulmonary circulation have important implications in hemodynamic changes during health and disease. **Figure 17.5** illustrates normal pressure/resistance relationship between various heart chambers and major vessels, which should be remembered while interpreting origin of clinical signs in heart diseases.

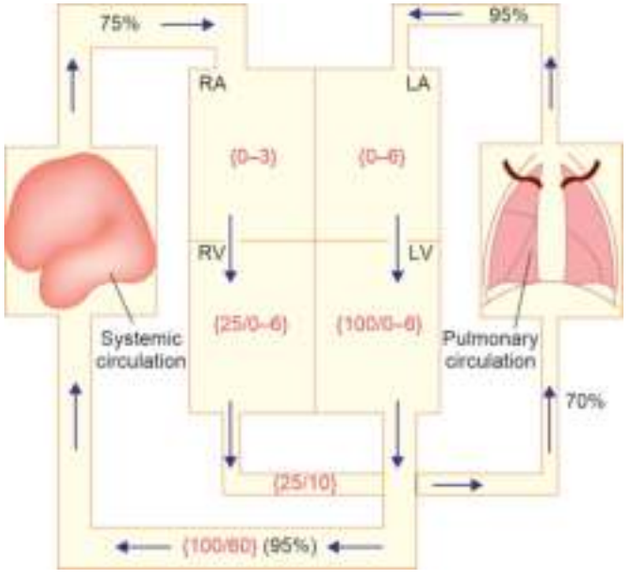


Fig. 17.5: Pressure relationships (mm Hg, in color) and oxygen saturation (% in black) in postnatal circulatory physiology.

17.2 CLINICAL EVALUATION FOR CARDIAC DISEASE

While presence of a 'murmur' is the most recognized indicator of underlying heart disease, it should be remembered that:

- All murmurs are not organic and functional murmurs are common in infancy due to relatively higher blood volume passing through small size valves and
- Absence of murmur does not exclude heart disease, which may be absent in large shunts or cardiomyopathies.

Clinical assessment for a cardiac disease includes a detailed history, thorough clinical examination and relevant investigations, discussed in following sections. Common clinical indicators of cardiovascular disorders are enumerated in **Table 17.1**.

History taking in a suspected heart disease, must concentrate on following symptoms, which provide valuable clues about the diagnosis, etiology and severity of a cardiac illness as well as presence or absence of complications.

Breathlessness (Dyspnea) is an important symptom of heart disease, indicating compromised oxygen supply to tissues either due to impaired myocardial function or altered pulmonary blood flow. It may be present throughout the day or develops only on exertion and may be graded according to *New York Heart Association* (NYHA) grades as follows:

Grade I: Dyspnea on unaccustomed exercise,

Grade II: Dyspnea on usual day-to day activity,

TABLE 17.1: Common indicators of CVS disease

- *Clinical history*
  - Unexplained failure to thrive
  - Ill sustained sucking on breast
  - Dyspnea on exertion or rest
  - Bluish discoloration on exercise/rest
  - Recurrent chest infections
  - Palpitation or chest pain
  - Syncopal attacks
- *Past history of rheumatic fever*
- *Family history of congenital heart disease*
- *Clinical signs*
  - CCF or LVF
  - Cyanosis or cyanotic spells
  - Abnormal heart sounds
  - Abnormal murmurs
  - Cardiomegaly
  - Abnormal BP
- *Signs of Co-existing disease*
  - Chromosomal/genetic disorders
  - Intrauterine infections
  - Other congenital defects
  - Rheumatic fever
  - Renal disease (hypertension)
  - Systemic infections (myocarditis/pericarditis)

Grade III: Dyspnea even at minor activity but not at rest,

Grade IV: Dyspnea at rest.

Severe dyspnea may also present as *orthopnea*, i.e., aggravation of breathlessness in lying down position. An orthopneic child prefers to sit on bed, even while in sleep.

Breathlessness in infants usually manifests with—(a) feeding difficulties, e.g. ill-sustained sucking or *suck-rest-suck cycle* with prolonged feeding time, and (b) feeding diaphoresis or *excessive sweating over forehead* due to sympathetic overstimulation due to exertion of feeding.

Chest pain is not uncommon in many heart diseases due to breathlessness. However, chest pain of specifically cardiac origin is usually localized over precordium or left shoulder and may be due to pericardial or myocardial involvement.

- Chest pain in pericarditis typically aggravates in supine position and relieves on sitting and leaning forward.
- Chest pain due to coronary involvement is common in children with severe aortic stenosis, ALCAPA (Anomalous coronary artery from pulmonary artery) or acquired coronary blockade, e.g. in vasculitis and hyperlipidemic states.

Palpitation refers to *patient's awareness or feeling of tachycardia*, usually in cases of impending/established CCF or arrhythmia. Palpitation is also common in high-output CCF, e.g. anemia, thyrotoxicosis, fever and other disorders of hyperdynamic circulation, e.g. AR or PDA.

Failure to thrive is common in cyanotic CHD or acyanotic CHD with increased pulmonary blood flow, due to poor feeding and breathlessness, leading to decreased oxygen and metabolic substrate supply for thriving. However, nutritional factors must be excluded in all cases.

Swelling (Edema) in heart disease is a sign of impending or established CCF, due to increased hydrostatic pressure and consequent leak of fluid in interstitial compartment. Cardiac edema typically – (a) begins from dependent parts of the body, i.e. sacrum in infants and dorsum of foot in older children, and (b) is more prominent in evenings after the whole day of cardiac exertion.

Bluish discoloration (Cyanosis) in a heart disease generally indicates right-to-left shunt (cyanotic heart disease), with following noteworthy features:

- Cyanosis is usually absent at birth in right to left shunts due to presence of PDA during first few days of life allowing enough flow to reach pulmonary circulation. These cases are also termed as duct-dependent and appearance of cyanosis indicates closure of ductus.
- Children with right to left shunts and substantial RV outflow obstruction often present with *cyanotic spells* (Ch 17.5.3).
- Appearance of cyanosis in a previously acyanotic child with left to right shunt may be an indicator of reversal of shunt or Eisenmengerization (C 17.5.2).

Fever in a cardiac disease may be an indicator of infective endocarditis or rheumatic fever, though may also be due to recurrent chest infections in presence of increased blood flow or coincidental causes.

Peripheral signs have important diagnostic values in a heart disease and must be assessed carefully before proceeding on cardiac examination. Important peripheral signs are as follows:

Pulse is usually assessed by three-finger palpation over radial artery at ulnar border of wrist, for: *(a) rate, (b) rhythm, (c) volume, (d) character, (e) tension.* In newborns or infants, heart rate (HR) is counted on chest rather than the pulse rate. Important characteristics of *pulse* include:

- ***Rate*** varies with age and physiological state, e.g. sleep and exercise. As a simple rule, normal HR is 120/minutes till 1 year of age; and then drops at a rate of 10/min/every 3 years, i.e. 110 at 3 years, 100 at 6 years, 90 at 9 years and 80 at 12 years.
  - *Tachycardia* may be physiological during exercise or excitement or pathological, e.g. fever, CCF, rheumatic carditis, myocarditis, early shock, arrhythmia, poisoning (atropine), etc.
  - *Bradycardia* may be physiological in athletes or pathological, e.g. enteric fever, heart blocks, raised intracranial pressure, digitalis toxicity, etc.
- ***Rhythm*** is normally regular, except respiration related variations-HR *decreases during inspiration* due to negative intrathoracic pressure > increased systemic venous return > better diastolic filling of RV > ↑stroke volume > ↓HR and *increases during expiration* due to positive intrathoracic pressure > reduced systemic venous return > reduced diastolic filling of RV > ↓stroke volume > ↑HR. For important rhythm abnormalities (arrhythmia), *see* Chapter 17.10.
- ***Volume*** of the pulse represents systolic blood pressure (BP) that normally *falls during inspiration* despite better diastolic filling of RV due to pooling of blood in expanded lungs > reduced pulmonary venous return > reduced LV stroke volume; and *increases during expiration* due to squeezing of lungs > increased pulmonary venous return and > increased LV stroke volume. Common abnormalities include:
  - *Low-volume pulse* in shock, aortic stenosis.
  - *Pulsus paradoxus* due to exaggerated inspiratory drop in BP and pulse volume during inspiration exceeding 10 mm Hg. This leads to complete disappearance of peripheral pulse during inspiration with an apparent difference between HR and pulse rate (*paradox*). It is seen in compressive conditions over heart, limiting diastolic filling during inspiration, e.g. constrictive pericarditis, CCF, status asthmaticus, tension pneumothorax, etc.

- ***Character:*** Normal pulse has a small, anacrotic '*a*' wave (early systole) followed by big tidal '*t*' wave on up-stroke (late systole) and a dicrotic notch '*n*' (closure of aortic valve) followed by a dicrotic '*d*' wave on down-stroke (reflected flow from closed aortic valve). Normally, only '*t*' wave is palpable. Common abnormalities of pulse character include:
  - *Thready pulse*, in impending shock.
  - *Water-hammer pulse*, i.e. a large bounding pulse that disappears suddenly, associated with wide pulse pressure (>40 mm) due to leak from arterial side (aortic run-off), e.g. in—(a) *cardiac causes*, e.g. AR, PDA, ruptured coronary sinus, etc. or (b) *peripheral causes*, e.g. large arteriovenous fistula, anemia, beriberi, etc. Water-hammer pulse is best felt at radial artery with elevated arm that accentuates arterial emptying by retverse flow.
  - *Anacrotic pulse*, i.e. slow-rising and low-volume pulse that appears to be beating twice due to prominent '*a*' wave, seen in aortic stenosis.
  - *Pulsus alternans*, i.e. alternate strong and weak pulses due to myocardial dysfunction, is seen in myocarditis, cardiomyopathy, left ventricular failure and supraventricular tachycardia.

Other abnormalities, e.g. *dicrotic pulse, pulsus bisferens*, etc. are rare in children.

Blood pressure (BP) should be recorded with appropriate methodology, discussed in Ch 17.12. Important BP characteristics in children include:

- Normal BP varies with age, sex and body size. American Academy of Pediatrics, 2017 has suggested age-and sex-dependent screening cut-off values for normal blood pressure in children, above which detailed evaluation is warranted (*see* **Table 17.39)**.
- Normal pulse pressure (SBP-DBP) is <25–30 mm Hg. *Wide pulse pressure of >40 mm indicates causes of water-hammer pulse*, discussed earlier.
- Systolic BP is ~5–10 mm less in inspiration than in expiration (*see* pulse-volume changes). *More than 10 mm drop in inspiratory BP indicates causes of pulsus paradoxus*, discussed earlier.
- BP in relative higher (~10 mm) in lower limbs than in upper limbs due to more muscle mass and consequently higher vascular resistance. *Higher BP in upper limb than in lower limbs, indicates coarctation of aorta, aortoarteritis, Takayasu disease, etc., while unequal BP in both arms suggests pre-ductal coarctation of aorta.*

Temperature must be recorded in all cardiac cases on admission and periodically for early diagnosis of superadded infections, e.g. pneumonia. Persistent mild to moderate fever may also be an indication of rheumatic fever or infective endocarditis.

Respiratory rate in a cardiac case is increased to maintain tissue oxygen supply despite compromised pulmonary perfusion in cases of increased or decreased pulmonary blood flow or impending or established CCF. RR varies with age and a RR of >60/min below 2 mo of age, >50/min from 2–12 mo and >40/min in older children is considered as abnormal.

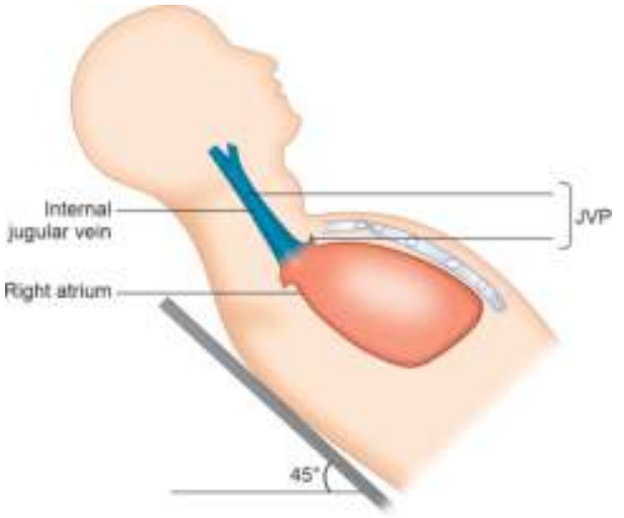


Fig. 17.6: Jugular venous pressure (JVP).

Jugular venous pressure (JVP) corresponds well with RA pressure, when assessed in semi-reclining position (45°) and measured correctly **(Fig. 17.6)**. JVP may be difficult to appreciate in young children, due to shorter neck and struggling child. It may be erroneously high in supine position or low in upright position. Important characteristics of JVP are:

- Normal JVP is 3–4 cm of water, *raised in:* (a) CCF, (b) constrictive pericarditis, (c) SVC obstruction, and (d) status asthmaticus.
- JVP changes with respiration, being less in inspiration (negative intrathoracic pressure facilitates venous return) than in expiration (high intrathoracic pressure opposes venous return). In pericardial tamponade, JVP rises paradoxically in inspiration due to raised intra-pericardial pressure (*Kussmaul's sign*).
- *Hepatojugular reflux*: If a pressure is applied over liver for 30 seconds, JVP initially increases due to the increased venous return but falls rapidly, due to the capacity of normal myocardium to accommodate extra blood. Sustained elevation of JVP (>1 minute) denotes positive hepatojugular reflux, seen in early CCF.
- Normal JVP consists of 3 positive (*a,c,v*) and 2 negative (*x,y*) waves. Unlike adults, these waves are difficult to appreciate in children, except in *tricuspid atresia, when giant 'a' waves* (due to atrial contraction against absent TV) are present.

Cyanosis, i.e. "bluish discoloration of nails and/or mucus membranes" indicates *increased amount of reduced hemoglobin (>5 gm/dl) in capillary blood*. Note that cyanosis may be absent in severe anemia despite severe hypoxia, due to low hemoglobin levels.

TABLE 17.2: Causes of cyanosis

- **Central cyanosis**
  - *Cardiac:* Rt to Lt shunt, Eisenmengerization
  - *Pulmonary:* Respiratory failure, severe asthma
  - *Abnormal Hb:* Methemoglobinemia, HbM disease
  - *Physiological:* High altitude
- **Peripheral cyanosis**
  - *Physiological:* At birth, cold exposure
  - Hypoxia
  - Circulatory shock
  - Polycythemia
- **Differential cyanosis**
  - PDA with shunt-reversal (only in lower limbs)
  - PDA with TGA (only in upper limbs)

TABLE 17.3: Causes of clubbing

a. Cardiac	Cyanotic CHD Infective endocarditis
b. Pulmonary	Bronchiectasis Lung abscess Fibrocaseous tuberculosis
c. GIT	Cirrhosis Ulcerative colitis
d. Others	Hereditary Traumatic

Clinically, cyanosis is best visible on nails and mucus membranes, e.g. lips, tongue and palpebral conjunctiva, with three clinical types **(Table 17.2)**:

- ***Peripheral cyanosis,*** visible on nails but not on mucus membranes, usually indicates local vascular stasis. Peripheral cyanosis is usually transient and disappears rapidly on warming/rubbing of limb to improve the local circulation.
- ***Central cyanosis,*** visible on nails as well as on mucus membranes, does not disappear easily with above measures. Central cyanosis may be due to pulmonary and cardiac etiology, further differentiated by *hyperoxia test*-reduction of cyanosis (or increase in PaO_2 >60 over basal value) after 100% oxygen inhalation for 10–30 minutes, indicates pulmonary etiology. Cardiac cyanosis does not improve substantially after hyperoxia test.
- ***Differential cyanosis*** is seen only in upper or lower limbs and indicates Rt > Lt shunt at PDA level.

Clubbing is the '*bulbous enlargement of the soft nailbed*', due to dilatation of underlying blood vessels, opening up of deep AV fistulas, and associated interstitial edema/tissue hypertrophy at finger-tips. Of varied etiology **(Table 17.3)**, exact stimulus for these changes is unclear, probably relates to localized tissue hypoxia due to septic/aseptic micro-emboli. While clubbing usually develops only after > 6 months of persistent pathology, it may develop within 4–6 weeks in infective endocarditis.

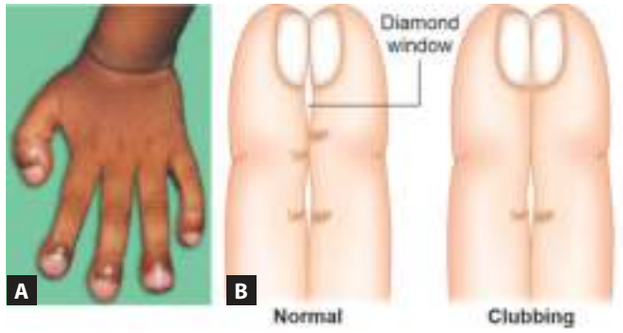


Fig. 17.7: Clubbing : (A) Clinical picture; (B) Schamroth sign.

Severity of the clubbing is graded as:

I. Softening of nail bed on palpation
II. Obliteration of angle at nail bed (*Schamroth sign*)*
III. Increased horizontal/vertical curvature of nails (*Parrot-beak* or *drumstick* appearance)
IV. Hypertrophic osteoarthropathy, i.e. painful swelling of hands/wrist with subperiosteal bone formation.

Schamroth sign: Opposition of dorsal surfaces of two opposite terminal phalanges normally leaves a diamond-shaped aperture that disappears in clubbing* *(Fig. 17.7)****.*

Other important peripheral signs in heart disease, e.g. arthritis, subcutaneous nodules, etc. in rheumatic fever or Osler nodes, Janeway lesions, etc. in infective endocarditis are discussed in respective chapters. .

Cardiac examination: Examination of heart includes *inspection, palpation, percussion and auscultation* over the precordium. Location-wise, various cardiac findings are denoted in terms of various precordial area **(Table 17.4)**. Note that these areas do not necessarily over-lie corresponding valves but represent the best sites to heart auscultatory abnormalities originating from them.

Inspection includes visual examination for: *(a) precordial bulge, (b) apex impulse, (c) pulsations, (d) dilated veins or other visible abnormalities.*

Precordial bulge may be due to*:* (a) cardiomegaly, (b) large pericardial effusion, and (c) recurrent chest infections suggestive of increased pulmonary blood flow.

Apex impulse*,* may not be well visualized in chubby children or pericardial effusion, *or* displaced in dextrocardia or ventricular hypertrophy.

Dilated chest veins indicate: (a) SVC obstruction, due to mediastinal mass, or (b) IVC obstruction, due to thoracic or abdominal lesions.

Visible pulsations may be diffuse (thin chest wall) or *localized* in tricuspid area/epigastrium (RVH), pulmonary area (PAH) suprasternal notch or neck (AR) or right hemithorax (dextrocardia).

Palpation confirms the inspection findings as well as provides additional information about: *(a) apex beat, (b) parasternal heave, (c) diastolic shock, and (d) thrill.*

TABLE 17.4: Precordial areas of clinical significance

Mitral	5th ICS, just inside midclavicular line
Tricuspid	Lower sternum, near xiphoid cartilage
Aortic	2nd ICS, parasternally on right side
Pulmonary	2nd ICS, parasternally on left side
Erb's	3rd ICS, parsternally on left side

ICS: Intercostal space

Apex beat is the outermost point of the cardiac impulse, normally located in 5th intercostal space within midclavicular line. It is relatively higher (4th space) in young infants due to small thoracic cage and developmental RV dominance. Important abnormalities include:

- *Abnormal location*:
  - Outward and downward in LVH.
  - Outward but not downward in RVH.
  - On right side in dextrocardia *or* dextroversion.
- *Abnormal character:*
  - *Tapping* (*localized*, forceful and ill-sustained) due to RVH, e.g. MS.
  - *Heaving* (diffuse, forceful and well-sustained) due to LVH with systolic overload, e.g. AS, MR.
  - *Hyperdynamic* (diffuse, forceful but ill-sustained) due to LVH with diastolic overload, e.g. AR.

Parasternal heave, i.e. palpable systolic impulse at left lower parasternal area indicates RVH.

Diastolic shock, i.e. palpable second heart sound (S_2) in pulmonary area indicates pulmonary hypertension.

Thrills, i.e. palpable murmurs, felt like *purring of cat* sensation indicate organic murmur >grade III **(*see* Table 17.6)** and interpreted accordingly.

Percussion is of limited value in children, except that—(a) left cardiac dullness, extending beyond the apex beat indicates pericardial effusion, and (b) dull note in left 2nd parasternal space indicates pulmonary artery dilatation suggestive of PAH.

Auscultation over precordium relates to—*(a) normal heart sounds, (b) abnormal sounds*, e.g. *opening snap, clicks and pericardial rub, and (c) murmurs.*

Normally, four heart sounds (HS) are produced during cardiac cycle, though III and IV HS are not easily audible, best recorded on phonocardiography.

First HS (S_1) denotes closure of atrioventricular mitral and tricuspid valves (MV/TV)) signifying end of the diastole. Normal S_1 is a low-pitched sound, best heard at mitral area. Important S_1 abnormalities include:

- *Loud S1* due to forceful closing of MV/TV, before complete emptying of atria in disorders with increased atrial volume, e.g. (a) MS/TS, (b) hyperdynamic states, e.g. anemia, thyrotoxicosis and (c) Lt > Rt shunts .
- *Soft or muffled S* due to inadequate closure of MV in-(a) MR, or (b) rheumatic carditis.

TABLE 17.5: Common S_2 abnormalities

Loud P_2	Pulmonary hypertension
Loud A_2	Systemic hypertension
Single S_2	
– due to absent P_2	Severe PS, TOF
– due to absent A_2	Severe AS
Fusion/reverse split (due to late A_2)	AS (outflow obstruction) AR, PDA (volume overload)
Wide and variable split	
– due to early A_2	VSD, MR
– due to delayed P_2	PS
Wide and fixed split*	ASD, TAPVR, severe MR

TAPVR: Total anomalous pulmonary venous return, **see* text

- *Absent S_1* due to tight MS.
- *Split S_1* in right bundle branch block due to delayed closure of TV.

Second HS (S_2) is produced by closure of semilunar aortic and pulmonary valves (AV/PV), signifying the end of systole. S_2 is best heard in pulmonary and aortic area, and has two distinct components – A_2 and P_2, corresponding to the closure of AV and PV respectively. As aortic ejection is more forceful due to thicker LV, AV closes earlier than the PV and hence, A_2 component is heard earlier than the P_2, leading to splitting of S_2.

Splitting of S_2 changes with respiration. *During inspiration, split is wider* due to negative intrathoracic pressure > pooling of blood in pulmonary vasculature > ↓ pulmonary venous return > ↓ LV end-diastolic volume > early closure of AV > early A_2. *During expiration, split is narrow or absent* due to increased intrathoracic pressure > ↓ systemic venous return > ↓ RV end-diastolic volume > early closure of PV > early P_2.

Intensity and splitting of S_2 has significant diagnostic value in cardiology **(Table 17.5)**. In ASD and total anomalous pulmonary venous return (TAPVR), atria are already dilated to maximum capacity, unable to accommodate extra flow during these respiratory changes. Hence, S_2 split is wide and fixed in these cases.

Third HS (S_3) is rarely audible in normal children and indicates rapid early diastolic filling of ventricles due to large atrioventricular pressure gradient, e.g. in MR, TR or CCF. It is best heard in left lateral position, just after S_2. Presence of S_3 is often indicated by *Gallop or Triple rhythm* — a bad prognostic sign in CCF.

Fourth HS (S_4) is produced by atrial contractions just before the S_1 and is rarely audible in children, except in *Ebstein's anomaly.*

Opening snap, heard in MS, is a sharp high-pitched sound at mitral area, immediately after S_2. It indicates snappy opening of MV to facilitate early-diastolic emptying of LV. Shorter the interval between S_2 and opening snap, more severe is the MS. Opening snap is absent in very tight MS or calcified MV.

TABLE 17.6: Grades of murmur

I	Inaudible, except on phonocardiography
II	Faint, but audible murmur
III	Easily audible murmur, but without thrill
IV	Murmur with thrill
V	Loud murmur, audible with ring of stethoscope
VI	Very loud murmur, audible even if stethoscope is lifted up from the chest wall

Systolic ejection clicks are high-pitched, click-like sounds in aortic/pulmonary area, immediately after S_1, due to forceful ejection of blood from overloaded ventricles into great vessels. Aortic ejection click, best heard in Erb' area (3rd Left parasternal space), indicates AS, severe AR or Coarctation of aorta. Pulmonary ejection click, best heard in pulmonary area during expiration, indicates PS or dilated pulmonary artery due to pulmonary arterial hypertension.

Pericardial rub, due to rubbing of inflamed pericardial layers in pericarditis, is audible in both systolic and diastolic phase. It may be differentiated from murmurs by—(a) scratchy character, (b) accentuation in sitting position and on pressure from stethoscope, and (c) rapidly changing character, not lasting for >2–3 days.

Murmurs indicate *turbulence in the blood flow* either due to-(a) normal flow across a narrowed valve or septal defect, or (b) increased flow across a normal valve in hyperdynamic states, e.g. anemia or in pathological shunts, e.g. VSD, PDA, etc.

All murmurs must be assessed for their—(a) *location* over precordium, (b) *relationship with cardiac cycle*, (c) *intensity* **(Table 17.6)**, (d) *character or pitch*, (e) *radiation* to other sites, e.g. axilla (MR), clavicle (PDA), neck (AS), etc., and (f) *changes with respiration, posture or other physiological events*.

Important effects of physiological events on murmurs include:

- Left-sided murmurs are prominent in expiration, as pulmonary venous return increases due to raised intrathoracic pressure. Right-sided murmurs accentuate in inspiration as systemic venous return increases due to negative intrathoracic pressure.
- All murmurs except in mitral valve prolapse (MVP) or hypertrophic cardiomyopathy (HCM) are louder in supine than in standing position. MVP and HCM murmurs are best audible in squatting position.
- All murmurs, except in severe HCM, become louder on exercise.
- Most murmurs, except in MVP and HCM, decrease in intensity and duration on Valsalva maneuver.

Murmurs of VSD, MR and AR (LV volume-overload) become louder when systemic vascular resistance is raised by inflating a BP cuff over the arm, 20 mm above the systolic pressure.

TABLE 17.7: Causes of functional murmurs

- **Developmental** (normal infants)
  - Still's murmur*
  - Axillary systolic murmur*
- **Hyperdynamic circulation**
  - Normal newborns
  - Severe anemia
  - Fever
  - Thyrotoxicosis
  - Beriberi
  - A-V fistula

**see* text

Etiologically, murmurs may be functional (without underlying heart disease) or organic.

Functional murmurs are present in ~15–20% infants, due to developmental immaturity or hyperdynamic states **(Table 17.7)**. These murmurs are characterized by – (a) soft systolic nature, (b) absence of thrill, (c) localized, and (d) absence of other abnormalities. Common functional murmurs in children are:

- *Still's murmur,* a mid-systolic murmur at apex and lower left sternal border with typical musical quality, e.g. vibrating string, produced by vibration of semilunar valves or ventricular walls.
- *Ejection systolic murmur* at pulmonary area, due to sudden opening of pulmonary valve. This murmur is more prominent in cases with severe anemia.
- *Systolic murmur* at axilla and back in newborns, due to sharp angulation of pulmonary arteries at the origin from common trunk.
- *Early systolic carotid bruit* over clavicles, due to sudden gush of blood in carotids.
- *Venous hum*-a low-pitched, soft, continuous murmur over jugular veins, is common in severe anemia. It is best heard in sitting position with head turn on opposite side, accentuated by exercise and obliterated by distal pressure over neck veins.

Organic murmurs are essentially associated with an anatomical or pathological defect in heart. Depending on their relationship with cardiac cycle, these murmurs may be divided into:

A. Diastolic murmurs are almost always organic and originate either during forward flow through atrioventricular valves (usually mid-or late-diastolic), *or* regurgitant flow through semilunar valves (usually early-diastolic). Common causes of diastolic murmurs are:

- *Early-diastolic* (EDM) in AR or PR.
- *Mid-diastolic* (MDM) in MS, TS or flow murmurs in VSD, MR and TR.
- *Late-diastolic* (LDM) in MS or TS.

Note that all named murmurs are diastolic, e.g.

- *Graham Steell's murmur*, an EDM in pulmonary area, due to pulmonary hypertension.
- *Carey Coombs murmur,* an apical MDM in rheumatic carditis, due to mitral valvulitis.
- *Austin flint murmur,* an apical MDM in AR, due to functional MS.

B. Systolic murmurs originate during the forward flow through semilunar valves (usually early-or midsystolic), the regurgitant flow through atrioventricular valves, or from Lt > Rt shunts (usually pansystolic). Systolic murmurs may be functional or organic, though presence of thrill almost always indicates an organic murmur. Common causes of organic systolic murmurs include:

- *Pan-systolic* (PSM) in VSD, MR or TR
- *Ejection systolic* (ESM) in AS, PS, TOF, or flow murmurs in AR and pulmonary hypertension.
- *Late systolic* (LSM) in mitral valve prolapse.

C. Continuous murmurs are heard in Lt > Rt shunts or aortic regurgitant lesions with large pressure gradient, that persists even during systole. Important causes of continuous murmurs include:

- PDA or aorto-pulmonary window,
- Blalock-Taussig shunt,
- ASD with MS (Lutembacher syndrome),
- AR *with* AS or VSD,
- Coronary AV fistula or ruptured sinus of Valsalva,
- Bronchial collaterals or AV fistulas, common in cyanotic CHDs.

17.3 INVESTIGATIONS IN CARDIAC DISEASE

Some important and specific investigations in cardiac disorders are as follows:

Chest X-rays provides valuable information about location and size of the heart as well as status of lung vascularity. In normal PA view, right border of the heart is formed by SVC, ascending aorta and RA; left border by aortic knuckle, pulmonary conus; cardiac apex by LV; and the base of cardiac silhouette by origin of great vessels. Chest X-ray in a cardiac case should be assessed for:

- ***Abnormal location*** of cardiac silhouette, e.g. dextrocardia, situs inversus or dextroversion. Abnormal location may also be due to non-cardiac causes, e.g. pneumothorax, collapse or diaphragmatic hernia.

  Normal situs is identified by—(a) gastric air bubble on left side, (b) higher dome of diaphragm on right side, (c) straight bronchus on right side. Reversal of these findings along with cardiac apex on right side indicates include situs inversus, while left-sided cardiac apex with normal situs indicates possibility of isolated Dextrocardia.
- ***Cardiomegaly,*** by calculating the cardio-thoracic (C:T) ratio, for which *thoracic width* is measured at widest internal thoracic point (C, **Fig. 17.8)** and *cardiac width* is measured from middle of the spine to ost distant cardiac show on Rt side + Left side (A+B, **Fig. 17.8)**.

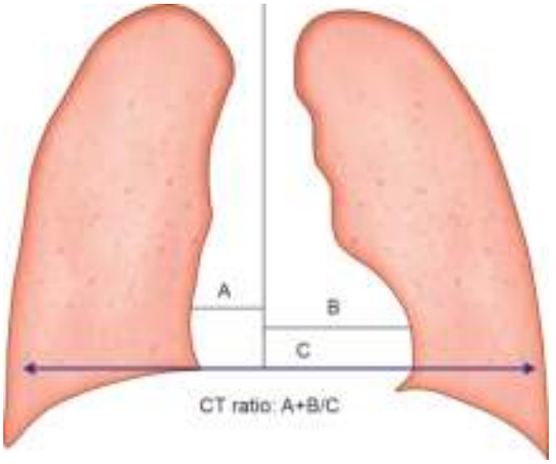


Fig. 17.8: Determination of cardio-thoracic ratio (CTR).

Upper limits of C:T ratio in normal children vary with age, being ~0.67 at birth, 0.61 at 1 year, 0.55 at 7 years and ~ 0.5 beyond this age, including adults.

Common causes of cardiomegaly on chest X-ray include—(a) CCF, (b) CHDs, (c) RHDs, (d) pericardial effusion, and (e) myocarditis/cardiomyopathies. Pericardial effusion may be differentiated from cardiomegaly due to CCF or organic heart diseases, on the basis of (a) typical *pear-shaped* cardiac silhouette, (b) narrow pedicle due to compression of great vessels, (b) oligemic lung fields, and (d) changing shape of cardiac silhouette in standing and decubitus exposures due to shift of fluid.

Heart size may appear reduced in chronic obstructive pulmonary disease (asthma/emphysema) and constructive pericarditis.

- ***Hypertrophy/dilatation of cardiac chambers***, as indicated by **(Fig. 17.9A and B)**:
  - Outward and downward shift of the apex in *LVH*
  - Outward but not downward shift of the apex in *RVH*
  - Bulging of right cardiac border in *RA dilatation*
  - *Dilatation of LA* is not directly visible on PA view due to posterior location of LA, but may be appreciated by—(a) straightening of left border (*mitralization),* (b) double-atrial shadow, (c) *lifting*-up of left bronchus, and (d) indentation of enlarged LA on esophagus in lateral barium-swallow plates.
- ***Status of pulmonary vascularity.*** In context of pulmonary vascularity, lung fields may be arbitrarily divided into three vertical sectors — the hilum, middle 1/3rd and outer 1/3rd of lung fields. Normally, pulmonary vessels are visible—*easily* at hilum, *seldom* in middle 1/3rd and *very rarely* in lateral 1/3rd of lung fields. Pulmonary arterial vasculature has better defined architecture on X-ray than pulmonary veins.

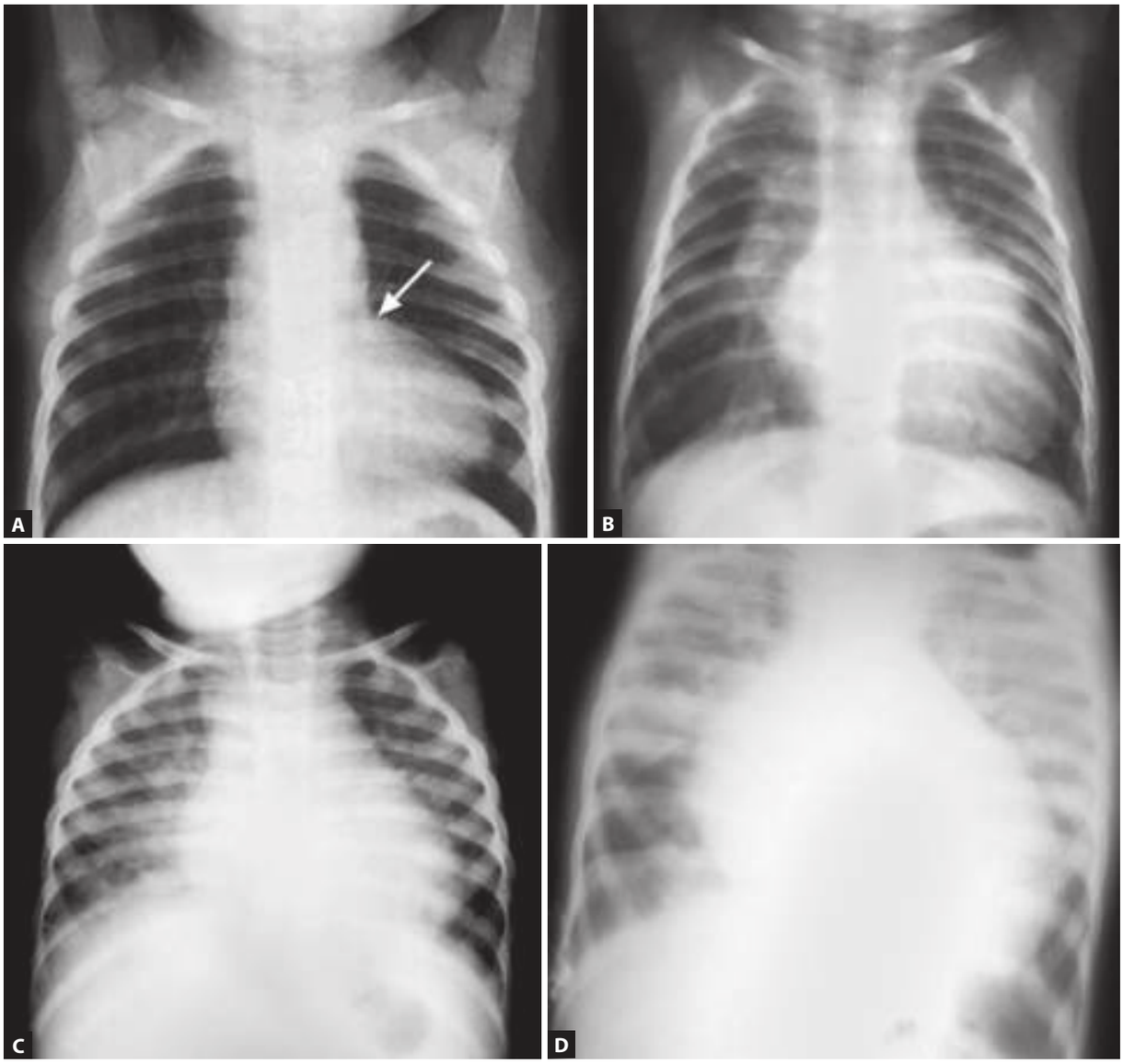


Fig. 17.9: Representative cardiac X-rays: (A) Right ventricular hypertrophy with oligemic lung fields; (B) Left ventricular hypertrophy; (C) Pulmonary arterial hypertension; (D) Pulmonary venous hypertension.

- *Pulmonary arterial hypertension* (PAH) is characterized by prominent hilum due to dilated pulmonary artery with outward fanning of linear vessels which taper suddenly (pruning) at the junction of middle and lateral third of lung fields, not extending up to periphery **(Fig. 17.9C)**.
- *Pulmonary venous hypertension* (PVH) is characterized by—(a) prominence of upper zone vessels and blurring of lower zone vessels, (b) generalized haziness extending from hilum due to interstitial edema *(bat-wing appearance)*, and (c) horizontal ribbon-like opacities due to engorged lymphatics and inter-septal edema, i.e. *Kerley-Fleischner lines* **(Fig. 17.9D)**.
- *Pulmonary oligemia*, i.e. decreased pulmonary blood flow, is more difficult to differentiate from normal, indicated by—(a) absence of pulmonary conus, and (b) relatively poor vascularity at hilum **(Fig. 17.9A)**.

Electrocardiography (ECG) is a 'graphic display of electrical conduction activity in heart', recorded on a special moving paper. Each small square on this paper represents 0.04 seconds on X-axis (duration) and 0.1 mV on Y-axis (voltage amplitude).

Normal electric activity in heart begins at sinoatrial (SA) node, travels through atrial walls to reach atrioventricular (AV) node, from AV node travels along the *bundle of His* in interventricular septum to reach ventricular walls through right and left bundle branches and Purkinje fibers.

TABLE 17.8: Adult and pediatric ECG: Imp. differences

- Tachycardia, with shorter PR interval, QRS complexes and QT interval
- Right QRS axis with RV dominance (tall R in V_{1-2}) in infancy
- Inverted T waves from 7th day to 7 years of life

Atrial contractions begin with activation of SA node while ventricular contractions begin only when AV node is activated. Thus there is a time-gap between atrial contractions represented by P wave and ventricular contractions represented by QRS complex; the gap denoted as PR interval.

Pediatric ECGs differ from adult ECGs on various aspects **(Table 17.8)** due to RV dominance at birth that declines with age. It is important to record a *13-lead ECG* in infants with an extra chest lead on right side (V_3R) to reflect actual RV status than V_{1-2} leads. In children, ECGs are mainly used to detect hypertrophy/overload of various heart chambers, apart from other problems, e.g. conduction defects, myocardial ischemia and electrolyte disturbances. ECGs should be assessed in a systemic manner, for following features:

a. **Heart rate** is calculated by dividing 1500 (small squares covered at regular paper speed in a minute) by number of small squares in P-P or R-R interval.

b. **Rhythm:** Normal cardiac rhythm is regular and originates from Sinoatrial (SA) node that acts as pacemaker. Electrical impulses from SA node travel to other parts of atrium > atrioventricular (AV) node > ventricular structures; and reflected on ECG as P > PR > QRS sequence.

   Rhythm abnormalities denote generation of abnormal rhythm either from normal site (SA node) or from abnormal site, (e.g. AV node), which may be identified on the basis of: (a) variable P-P or R-R interval, (b) altered relationship between P and R waves, and (c) altered configuration of P waves, as follows:
   - *Absence or abnormal shape/axis of P wave* indicates: (a) ineffective rhythm generation at SA node (atrial fibrillation), (b) non-conduction of SA node impulse (sinoatrial block), or (c) rhythm generation outside the SA node (AV nodal rhythm).
   - *Multiple P waves preceding QRS complex* indicate - (a) excessive rhythm generation at SA node (atrial fibrillation, atrial flutter), or (b) failed conduction through AV node (AV blocks).

c. **P wave** represents *atrial depolarization*. It is normally upright in all leads except aVR and does not exceed 3 mV in amplitude and 0.12 second in duration. Common P wave abnormalities are:
   - Tall and peaked (*P pulmonale*) in RA enlargement.
   - Wide and notched (*P mitrale*) in LA enlargement.
   - Absent/multiple P waves per QRS in arrhythmia.
   - Inverted P waves (Lead I) in dextrocardia or incorrect placement of electrodes.

d. **PR interval,** from onset of P to onset of R wave, indicates *physiological delay in AV conduction.* Although varies with age and HR. Normally, it should be <0.08 second up to 3 years and <0.12 seconds in older children. Common abnormalities include:
   - *Prolonged* PR interval in myocarditis including rheumatic fever, digitalis toxicity, hyperkalemia, endocardial cushion defect.
   - *Decreased* PR interval in WPW syndrome, glycogen storage disorders, etc.

e. **QRS complexes** represent *ventricular depolarization*. Normal *QRS interval* increases with age but does not exceed 0.12 second at any age (<0.08 second in infants). Common QRS complex abnormalities include:
   - *Low-voltage* QRS (<5 mm in limb leads or <10 mm in chest leads) in pericardial effusion, hypokalemia, hypothyroidism, *etc*.
   - *Large* QRS in RVH/LVH.
   - *Wide* QRS (>0.12 second) in conduction defects, e.g. bundle branch blocks.
   - *Abnormal configuration* (rSR or M pattern) in myocarditis, cardiomyopathy, bundle branch block.

   Normally, **Q waves** are visible only in left-sided chest leads (V5–6). Important Q wave abnormalities include:
   - Presence of Q waves in V_{1-2} in severe RVH.
   - Deep Q waves (> 5 mV) in V_{5-6} in LVH.
   - Absent Q wave in V_{5-6} in dextrocardia or LBBB.
   - Deep and wide Q waves in myocardial ischemia.

f. **ST segment** represents time between depolarization and repolarization and should be assessed for elevation/depression from isoelectric line (>1 mm). Important ST segment abnormalities include:
   - *Elevated* in early pericarditis, digoxin toxicity (*tick sign*) and myocarditis.
   - *Depressed* in pericarditis with effusion, cardiomyopathies or myocardial ischemia due to any cause, e.g. severe anemia, anomalous coronary vessels, severe hypoxia, etc.

g. **T waves** represent ventricular depolarization and its configuration changes with age. T waves are upright or flat at birth, turn negative by 7th day and remain so till 7–8 years before becoming positive again, (may remain negative in V_{1-2}). Common T wave abnormalities include:
   - Upright T wave in V_{1-2} (7 days – 7 years) in RVH,
   - Flat/inverted T waves (>7 years, except in V_{1-2}) in pericardial effusion, myocarditis, digitalis toxicity, hypokalemia and LVH/strain,
   - Tall T waves (tent-shaped) in hyperkalemia.

h. **QT interval,** from beginning of the Q wave to the end of T wave, represents total duration of ventricular systole. As it varies with HR, corrected QT

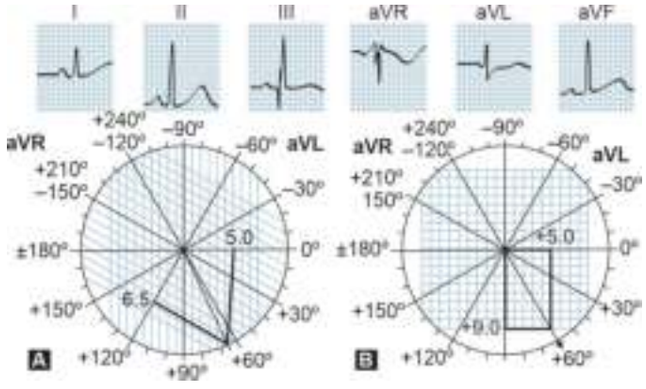


Fig. 17.10: Graph method for ventricular axis.

interval (QTc), i.e. QT interval/RR interval, is more informative, normal being < 0.44 second. QTc is:

- Increased in long QT syndrome, myocarditis, Rh carditis, hypocalcemia and quinidine
- Decreased in digitalis effect and hypercalcemia.

i. **U waves** denoting slower repolarization of Purkinje's fibers and papillary muscles, are rarely visible after T wave with similar polarity. Inverted U waves in children indicate digitalis toxicity, pulmonary embolism and LV overload.

j. **QRS axis** is calculated using only the limb leads, by any of the two methods, discussed below. ECG in **Fig. 17.10** has been used as example for both methods.

a. Graph method **(Fig. 17.10)**:

- Find net QRS amplitude {(+R) + (+S)} in any two leads, e.g. L1 and L3. In given example, net amplitude in L1and L3 is {(+5.5) + (–0.5) = +5.0} and {(+10.0) + (–3.5) = (+6.5)}
- Plot it on corresponding axis of each lead over graph paper.
- Draw perpendiculars to these axes, passing through these two points.
- A line connecting intersector of these perpendiculars with the center represents QRS axis. In given example it is + 65°.

b. Successive approximation method is simple, based on hexaxial reference system **(Fig. 17.11)**:

- Locate the main quadrant of axis, using net pattern of QRS complexes in lead I and aVF. In given example, net positive deflections in lead I and aVF indicate that axis is between 0 and +90.
- Find a lead with equiphasic QRS complex (aVL in example). The QRS axis is perpendicular to this lead and lies within the pre-determined quadrant. In given example it is +60°.

Some characteristics ECG abnormalities in various chamber hypertrophies are shown in **Fig. 17.12**.

Echocardiography is an extremely valuable *diagnostic tool* for—(a) direct visualization of cardiac anatomy, (b) evaluation of pressure gradients across various valves

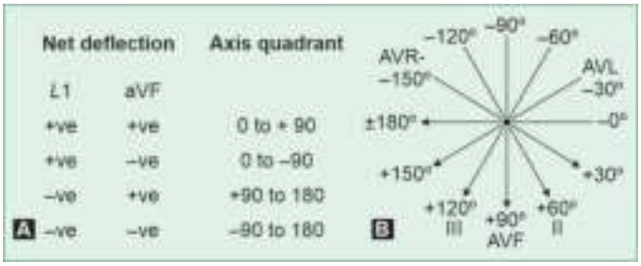


Fig. 17.11: Hexaxial method for ECG axis determination: (A) Location of axis; (B) Hexaxial system.

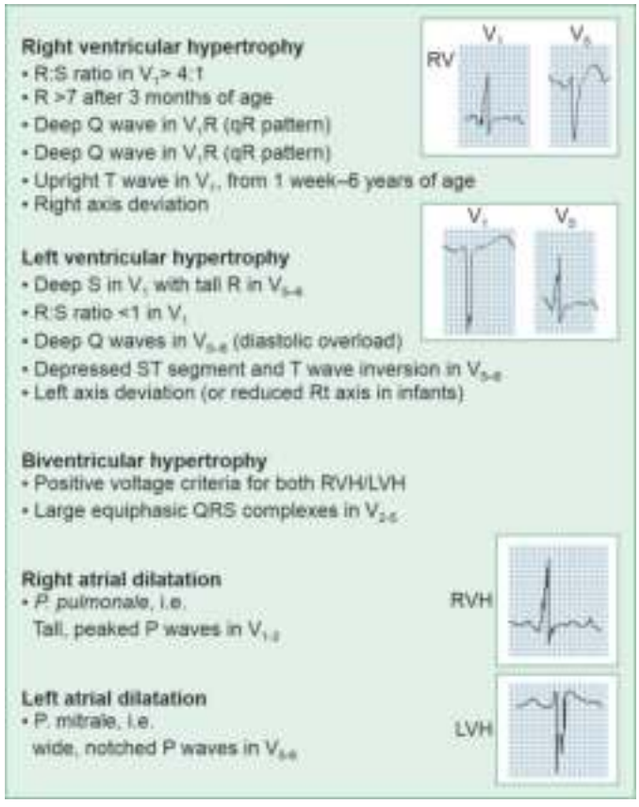


Fig. 17.12: ECG findings in cardiac chamber hypertrophies.

and vessels, (c) assessment of blood flow through shunts, (d) assessment of myocardial functions, and (e) visualization of vegetations, pericardial fluid or intracardiac thrombi, tumors, etc. In addition, it is also useful for—(f) pericardiocentesis and (g) balloon septostomy and other interventional procedures.

Fetal echocardiography may identify CHDs as early as by 17–19th weeks of gestation and is routinely recommended in pregnancies with history of previous child or first-degree relative with CHD.

Echocardiography includes various procedures, e.g.

- ***M-Mode Echo*** is a one-dimensional slice of cardiac structures to provide information about anatomy and mobility of valves, measurement of cardiac dimensions and assessment of myocardial contractility. Later is usually denoted in terms of % fractional shortening in LV dimensions during end-systole compared to that

in end-diastole (LVED – LVES/LVED 100), normal being 30–40%.

- ***Two-D echo*** provides flexibility of reconstructing multiple real-time images using different views for different cardiac structures. Accuracy of 2-D echo has obviated the need for invasive studies, e.g. cardiac catheterization in many cardiac lesions.
- ***Three-D echo*** is used to measure volume and ejection fraction of unusual ventricular geometries and visualize device placement
- ***Doppler echo*** displays the volume, speed and direction of blood-flow across various cardiac chambers and vessels, based on the change in frequency imparted to a sound wave by the movements of blood cells, using either *pulse* (intermittent) or *continuous wave* Doppler technique. It is most useful to assess—(a) severity of intracardiac shunts, (b) adequacy of systemic/pulmonary blood flow, (c) pressure gradients across valves, and (d) reversal of flow in valvular insufficiency.
- ***Trans-esophageal echocardiography*** is an extremely sensitive method to visualize small vegetations in infective endocarditis, posteriorly-located lesions and for intra-surgery monitoring.

Cardiac catheterization is a valuable diagnostic and therapeutic tool in cardiology, involving percutaneous passage of a soft, flow-directed, balloon-tipped catheter into RA through femoral/jugular vein, under fluoroscopic guidance. From RA, catheter is further advanced to RV and then to LA/LV via formen ovale.

Left side of heart may also be reached by retrograde passage of catheter from femoral artery. During catheterization, following procedures may be conducted—(a) collection of blood samples from different chambers to measure oxygen saturation and calculate shunt volumes, (b) measurement of various chamber pressures to calculate transvalvular gradients, (c) injection of a contrast media to selectively delineate cardiac structures, and (d) special procedures, e.g. angiocardiography, balloon angioplasty or valvoplasty, etc.

Indications for cardiac catheterization in children generally include:

- *Diagnostic:*
  - Pre-surgery evaluation of anatomy and shunt size
  - Evaluation of pulmonary vascular resistance and its responsiveness to drugs/oxygen
  - Post-surgery follow-up in CHDs
- *Therapeutic* (interventional cardiology)
  - Balloon valvuloplasty, i.e. dilatation of stenotic valves, e.g. PS, AS, etc.
  - Balloon angioplasty, i.e. dilatation of coarcted aorta or pulmonary branch stenosis with coils/stents.
  - Embolization of abnormal communication, e.g. PDA.
  - Closure of septal defects, e.g. small/medium ASDs and muscular VSDs, using umbrella, button or clamshell devices.

Complications include aneurysms, infection, arrhythmia and thromboembolic episodes. Lesions underwent balloon valvuloplasty/angioplasty are more likely to get re-stenosed than open-operated cases.

Cardiac magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) provide tomographic images of the heart in different projections with excellent contrast resolution, permitting assessment of myocardial thickness, chamber volumes, valvular functions and even blood flow velocity/volumes. Being non-invasive modalities, these investigations have gradually replaced the need for diagnostic cardiac catheterization in many cases, specially post-surgical follow-ups.

MRI is particularly useful to evaluate areas not well visualized by echocardiography, e.g. distal pulmonary artery anatomy and anomalies in systemic and pulmonary venous return. Computerized processing of MRA images allows the noninvasive visualization of the cardiovascular system from inside of the heart or vessels, a technique known as *fly-through* imaging.

Blood investigations in a cardiac disease not only help in assessing the etiology of disease but also to assess the severity and response to treatment (ESR in rheumatic fever) and presence of complications, e.g. polycythemia or metabolic defects in cyanotic CHDs. However the choice of tests depends on the clinical possibilities, with some general suggestions as follows:

- All cases on first contact should be assessed for baseline hematological investigations, e.g. Hb, total count, platelet count (Kawasaki disease), etc.
- Suspected rheumatic fever needs additional ESR, CRP, ASLO and throat swab to assess the presence of rheumatic fever.
- Suspected infective endocarditis requires at-least three blood cultures at different times as discussed in relevant chapter to identify the microbial etiology.
- Suspected myocarditis cases need Troponin and CPK-MB levels to quantify the extent of tissue damage, apart from virological studies to identify etiology.
- Suspected cardiomyopathies need metabolic/enzyme studies as well as endocrinal workup, as required.

17.4 CONGESTIVE CARDIAC FAILURE

Congestive cardiac failure (CCF) is characterized by "*Inability of the heart to maintain adequate cardiac output, at rest or during stress, necessary for the metabolic needs of body*".

Pathogenesis: Adequacy of cardiac output (COP) depends on three important factors—(a) adequate

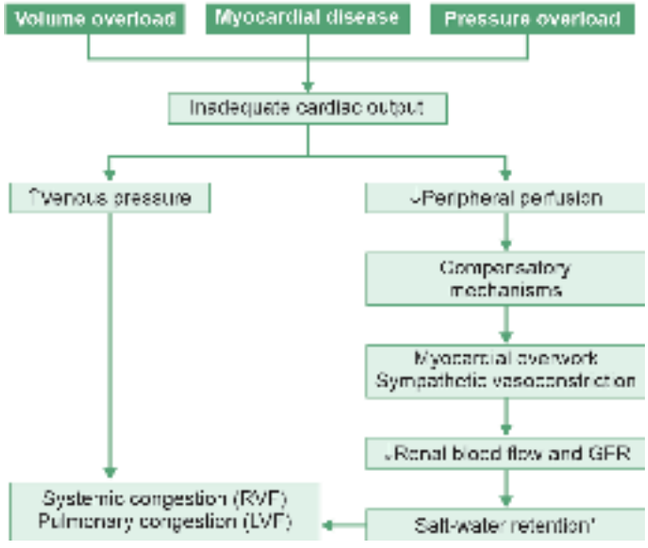


Fig. 17.13: Pathophysiology of CCF.
*renin-angiotensin/aldosterone mediated

diastolic filling (pre-load), (b) adequate myocardial contractility, and (c) unhindered forward flow to systemic/pulmonary circulation (after-load).

Abnormality in any one or more of these COP regulatory factors, i.e. increased diastolic filling (*volume overload*), poor myocardial contractility or obstruction in ventricular outflow tracts (*pressure overload*) may progress to CCF, specially if compensatory mechanisms fail **(Fig. 17.13)**.

Volume overload is usually caused by left to right shunts or regurgitant lesions, leading to overdistension of ventricular chambers. Since dilated ventricles fail to accommodate further venous return, these cases are also termed *diastolic failure or backward failure.* Although distended ventricles contract more forcefully (Frank-Sterling law) to maintain stroke volume, at one stage this Frank-Sterling relationship fails and ventricles dilate to precipitate CCF.

Pressure overload is usually caused ventricular outflow obstruction, e.g. in AS, PS, COA, etc., leading to increase in myocardial contractility as well as increase in heart rate to compensate falling cardiac output (COP = Stroke volume × Heart rate). However, these compensatory mechanisms, when fail, also precipitate CCF due to-(a) increased myocardial oxygen demand and consequent myocardial hypoxia, and (b) Lower stroke volume, as tachycardia does not allow enough time for ventricular filling in diastole. Since primary abnormality in these cases is poor systolic ejection despite adequate diastolic filling in early stages, it is also termed *systolic failure or forward failure*.

Primary myocardial dysfunction due to hypoxia, sepsis, arrhythmia, etc. leads to: (a) decreased stroke volume due to impaired myocardial contractions, (b) Compensatory tachycardia with further hypoxia and decreased diastolic filling time, and (c) Peripheral vasoconstriction with increase peripheral vascular resistance to maintain sufficient blood pressure and ensure adequate tissue perfusion. This compensation is also accompanied by redistribution of blood flow from non-vital (cutaneous/muscular) to vital (brain, myocardium and kidneys) organs. However, vasoconstriction further aggravates after-load to contribute in CCF pathology.

In some cases with poor oxygen carrying capacity, e.g. severe anemia *or* increased oxygen demand, e.g. fever, infection, thyrotoxicosis, etc., metabolic demands cannot be met despite normal or even high COP, leading to ***high output CCF.***

TABLE 17.9: Causes of CCF in children

Primary (Cardiac) causes
- Congenital heart diseases*
- Rheumatic fever/Rheumatic heart disease
- Constrictive pericarditis
- Myocarditis and cardiomyopathies
- Infective endocarditis
- Endocardial fibroelastosis
- Arrhythmia
- Systemic hypertension

Secondary (Extra-cardiac) causes
- *Hypoxia:* Birth asphyxia*, Cor-pulmonale
- Severe anemia*
- Septicemia*
- *Metabolic:* Hypoglycemia, hypocalcaemia
- Fluid overload—Iatrogenic*, acute glomerulonephrtitis

*Common causes in newborns

Etiology: CCF may develop due to primary cardiac abnormalities *or* following secondary dysfunction of myocardium or peripheral vascular tone **(Table 17.9)**. Relative frequency of etiological factors for CCF varies with age **(Table 17.10)** with some important considerations as follows:

- CCF in first few days of life is more likely due to the non-cardiac than cardiac causes. Subsequently, CHD is the leading cause of CCF till 5 years of age and rheumatic fever or RHDs beyond this age
- Among the structural heart lesions, those with more severe outflow obstruction or regurgitation present earlier than moderate or milder defects. Valvular atresia usually present in newborns.
- Left to right shunts usually do not present with CCF in first few weeks due to higher pulmonary resistance and right ventricular pressures, preventing significant shunting.

Clinical manifestations of CCF vary according to its severity, duration, predominant ventricular involvement and age of the child. Important clinical features include:

- ***Signs of RV failure*** (systemic venous congestion)
  - Edema, specially on dependent parts, e.g. sacrum in infants and feet in older children.

TABLE 17.10: Common causes of CCF at different ages

< 1 week	– Extracardiac: Hypoxia, sepsis
	– Valvular atresia: TA, PA, AA, COA
	– Lt/Rt hypoplastic heart syndrome
	– PDA (in preterms)
1 week – 1 month	*All above, plus*
	– Severe obstructive lesions — PS, AS, CoA
	– Large L>R shunts — VSD, PDA
	– Large R>L shunts — TrA, TGA, SV
1 month – 1 year	*All above, plus*
	– Moderate L>R shunts — VSD, PDA,
	– Moderate R>L shunts — TGA, TAPVR
	– Endocardial fibroelastosis
	– Myocarditis and cardiomyopathies
	– Pericarditis
1–5 years	*All above, plus*
	– Infective endocarditis
>5 years	– CHDs—smaller shunts/obstructive lesions
	– Rheumatic fever/rheumatic heart disease
	– Hypertension, e.g. acute glomerulonephritis

TA: Tricuspid atresia; **PA:** Pulmonary atresia; **AA:** Aortic atresia; **CoA:** Coarctation of aorta; **PDA:** Patent ductus arteriosus; **TrA:** Truncus arteriosus; **TGA:** Transposition of great arteries; **SV:** Single ventricle; **TAPVR:** Total anomalous pulmonary venous return.

  - Hepatomegaly, often tender and soft
  - Raised JVP, which may be difficult to appreciate in infants due to smaller neck.
- ***Signs of LV failure*** (pulmonary congestion)
  - Ill-sustained sucking (suck-rest-suck cycle)
  - Dyspnea on exertion or rest
  - Recurrent chest infections
  - Tachypnea or dyspnea
  - Basal crepitations on auscultation
- ***Signs of myocardial stress or dysfunction:***
  - Tachycardia, muffled heart sounds, gallop rhythm
  - Cardiomegaly
- ***Signs of inadequate cardiac output:***
  - Hypotension
  - Irritability/syncope (↓CNS perfusion)
  - Oliguria (↓renal perfusion)
  - Failure to thrive in chronic cases
- ***Signs of compensatory sympathetic activity:***
  - Thready, low-volume pulse or pulsus alternans
  - Cool, cyanosed extremities (peripheral vasoconstriction)
  - Excessive perspiration over forehead, specially during feeding, is an important sign of CCF in infancy.

TABLE 17.11: Common indicators of CCF in infancy

- Feeding difficulty (suck-rest-suck cycle)
- Failure to thrive
- Recurrent chest infections
- Persistent tachypnea and tachycardia
- Hepatomegaly
- Facial puffiness/sacral edema
- Excessive perspiration over forehead
- Cardiomegaly

- ***Signs of primary or causative disease:***
  In newborn and infants, typical features of CCF may not be as obvious as in older children, specially when cardiac lesion is not apparent **(Table 17.11)**.

Diagnosis: Apart from the age of presentation, etiological diagnosis in CCF depends on clinical examination and relevant investigations, e.g. chest X-ray (cardiomegaly with/without pulmonary plethora), ECG (chamber hypertrophies) and Echocardiography. Cases without a known cause or structural lesion, also need detailed workup for possible etiologies, e.g. sepsis screen, metabolic and electrolyte abnormalities, Cardiac enzymes, e.g. troponin, CPK-MB, Viral panels for myocarditis, etc.

Clinically severity of the CCF may be classified as per ***Modified Ross Classification***, as follows:

- **Class I :** No symptoms/limitations;
- **Class II:** Tachypnea and dyspnea on exertion (sweating during feeds in infants) *but no growth failure.*
- **Class III:** Tachypnea and dyspnea on exertion (sweating during feeds in infants) with *growth failure.*
- **Class IV:** Symptoms at rest, e.g. tachypnoea, retractions, grunting and sweating, *with growth failure.*

Although rarely needed, ***severity of CCF*** or ventricular dysfunction may also be monitored on echocardiography by—(a) *Fractional shortening* of ventricles on echocardiography, normal being 28–40%, (b) *Ejection fraction* (end systolic volume – end diastolic volume/end diastolic volume) by Doppler studies or cardiac catheterization, normal being 55–65%, and (c) *Pre-ejection time: Ejection time ratio* on M-mode echocardiography, normal being <40%.

Management of CCF aims to—(a) reduce metabolic oxygen demands, (b) maximize oxygen supply, (c) decrease preload, (d) increase myocardial contractility, (e) decrease afterload, and (f) treat the primary cause. Important steps in management include:

- **Supportive therapy** mainly aims to reduce the oxygen and metabolic demands of body, by:
  - *Bed rest:* Complete bed rest is rarely needed except in severe cases, though strenuous activity should be avoided.
  - *Positioning:* Baby should be nursed in propped-up position to maximize lung expansion and reduce systemic venous return.

- *Sedatives*, e.g. chloral hydrate may be used in restless child, unless respiratory depression is present.
- *Oxygen supplementation* should be provided to maximize hemoglobin saturation. However, Oxygen may deteriorate Left to right shunts due to pulmonary vasodilatation.
- *Diet:* High-caloric (120–150 cal/kg), low-volume (100 ml/kg), low-sodium diet (max 1 gm/day) is advisable, though water restriction is rarely needed.
- *Correction of high metabolic states*: Fever, severe anemia, infections are common causes of refractory CCF and needs to be treated promptly. Blood transfusion is indicated only in cases with Hb < 7 gm/dl.

- **Diuretics** are first-line drugs in CCF, used to reduce the preload over ventricles. Choice of the diuretic and route of therapy depends on severity of CCF and pulmonary congestion.

  IV/PO Furosemide (1–2 mg/kg/day) is the preferred choice in severe cases. Hypokalemia is the most important complication of furosemide therapy, which may be prevented by oral potassium supplements (1–3 mEq/kg/day). Long-term use of furosemide may also cause volume depletion and contraction alkalosis.

  PO Chlorothiazide (20–50 mg/kg/day) alone or with a potassium-sparing diuretic, e.g. spironolactone (3 mg/kg/day) is preferred in mild/moderate CCF to avoid the risk of hypokalemia.
- **Digoxin** continues to be commonly used in management of CCF in children despite some controversies, *except in high-output cardiac failure and pericardial temponade*. It acts by—(a) improving the myocardial contractility (inotropic effect), and (b) reducing the heart rate, to improve ventricular filling

  Therapeutic effect of Digoxin (Digi-effect) is apparent within 4–6 hours with-(a) reduction in heart rate, (b) clinical improvement in signs of CCF, and (c) ECG changes, e.g. prolongation of PR interval. However, sustained effect requires Digitalization with multiple doses either *rapidly* (24 hours) or *slowly* (7 days) depending on the urgency, followed by maintenance therapy **(Table 17.12)**. Slow digitalization is safer but time-consuming and in most children, rapid digitalization is necessary either by IV or PO route.

  Digoxin has a very narrow therapeutic range and toxicity is common in preterms, myocarditis, dyselectrolytemia and impaired renal functions **(Table 17.13)**. Hypokalemia, due to concomitant furosemide therapy also aggravates digoxin toxicity. Following precautions are necessary in all cases on digoxin therapy:
  - Loading dose should not be used in cases, who are already on digoxin therapy,
  - IV dose should not exceed 2/3rd of the Oral dose.
  - Lower doses should be used in Preterms and term newborns.
  - Maintenance dose must be skipped once or twice a week to avoid cumulative toxicity (given only 5–6 days a week).
  - *HR <60/minute is the earliest indicator of digoxin toxicity* and calls for immediate discontinuation of drug. Serum digoxin levels >2 ng/ml, though not necessarily reliable in children, indicate potential risk of toxicity.

  Management of digoxin toxicity includes-(a) Immediate discontinuation of drug, (b) Electrolyte estimations, (c) IV/PO potassium supplements (2–3 mEq/kg/day), (d) IV dilantin, 3–5 mg/kg every 10–15 minutes till HR returns to baseline, and (e) Calcium chelaters, e.g. IV EDTA infusion (15 mg/kg/hr in DW5%) in hypercalcemic cases.
- **Inotropic agents** like β-*agonists* (Dopamine, Dobutamine), *phosphodiasterase inhibitors* (milrinone, amrinone) or calcium sensitizers (Levosimendan) are being increasing used for initial control of CCF. Apart from inotropic effect, these drugs cause peripheral vasodilatation and reduce the afterload.
  - Low-dose Dopamine (2–10 µg/kg/min) is the most frequently used inotrope, with added benefits of afterload reduction due to peripheral vasodilatation and diuresis following selective renal vasodilatation. However, higher doses (>10 µg/kg/min) may cause vasoconstriction with consequent rise in afterload and should be avoided.

TABLE 17.12: Digitalization in children

Rapid oral digitalization:
Total digitalizing dose (TDD) 0.04 mg/kg*
– First dose (½ TDD) 0.02 mg/kg
– Second dose (¼ TDD) 0.01 mg/kg after 6–12 hrs
– Third dose (¼ TDD) 0.01 mg/kg after 12–24 hrs
– Maintenance dose# 0.01 mg/kg/day
Rapid IV digitalization 2/3rd of oral dose
Slow digitalization 0.01 mg/kg/day from beginning

*Generally used, Higher TDD in 1 mo-1 yr age: 0.06–0.08 mg/kg
#Start after 24 hours of Last (3rd) digitalizing dose

TABLE 17.13: Signs of digoxin toxicity

Cardiac	Bradycardia
	Arrhythmia
Non-cardiac	Vomiting, diarrhea
	Visual hallucinations
ECG	Prolonged PR interval
	ST segment elevation
	T wave inversion

  - IV Dobutamine (2–20 µg/kg/min), though less effective than dopamine as an inotrope, causes less tachycardia or peripheral vasoconstriction. It is generally used in cases not responding to upper limit doses of dopamine. Dobutamine is also the preferred choice for CCF due to cardiomyopathy and other myocardial dysfunctions.
  - IV Milrinone (0.3–0.7 µg/kg/min) has powerful inotropic and peripheral as well as pulmonary vasodilatory effect, though adverse effects, e.g. thrombocytopenia and hypotension, limit its use only in select refractory cases.
  - IV Levosimendan (6–12 µg/kg Loading dose over 10 minutes followed by 0.05–0.2 µg/kg/min) is a potent inodilator with systemic as well as coronary vasodilation without side-effects of milrinone, emerging as preferred choice in many intensive care settings.
- **Afterload reducing agents,** e.g. *ACE inhibitors* (captopril, enalapril), *arteriolar dilators*, e.g. hydralazine and *arterio-venous dilators*, e.g. nitroprusside, act by reducing systemic vascular resistance (afterload). These drugs are *indicated* in refractory CCF with large Lt > Rt shunts, severe regurgitant lesions, e.g. MR/AR, cardiomyopathy and hypertension, while *contraindicated* in stenotic lesions, e.g. AS, COA, renal artery stenosis, etc. or in renal failure.

  Enalapril is the preferred ACE inhibitor, (0.1–0.5 mg/kg/day q12hr) for long-term control of CCF. Sodium nitroprusside (0.5–0.8 µg/kg/min) is used only in critically sick cases, though has been largely been replaced by milrinone and levosimendan for the additional inotropic effect. Data regarding use of angiotensin receptor blockers, e.g. Losartan in CCF is limited in children.
- **Beta-blockers,** e.g. propranolol or atenolol, may be useful in selected cases of chronic CCF, e.g. cardiomyopathies, by—(a) increasing myocardial contractility, and (b) preventing the cardiotonic effects of catecholamines. However, their exact role in routine anti-CCF therapy is not established.

  Carvedilol (0.1–0.8 mg/kg/d q8hr), a non-selective beta-blocker commonly used in adult CCF is useful in selected case of cardiomyopathy and for persistent ventricular dysfunction after cardiac surgery, (e.g. ALCAPA repair), though data is limited.
- **Mechanical measures,** e.g. extracorporeal membrane oxygenation, intra-aortic balloon pumping, biventricular pacing, etc. are reserved for selected cases of refractory CCF, awaiting cardiac surgery or transplant.
- **Treatment of underlying cause:** CCF, refractory to medical therapy needs re-evaluation and search for underlying cause **(Table 17.14)**. Active rheumatic carditis and infective endocarditis are two leading causes of refractory CCF in children.

TABLE 17.14: Causes of resistant CCF

- Active rheumatic carditis
- Infective endocarditis
- Co-existing lung or other infections
- *High-output states* : Fever, exercise, anemia
- *Dyselectrolytemia* : Acidosis, hypokalemia, hyponatremia, hypercalcemia
- Pulmonary embolism

Prostaglandin E_1 infusion (0.05 µg/kg/min) may be very useful in ductal-dependent lesions, e.g. Left hypoplastic heart syndrome or TGA, till further interventions are possible.

17.5 CONGENITAL HEART DISEASE

Congenital heart diseases (CHD) are present in ~8–12/1000 live births, though the true incidence is perhaps much higher, as many of them remain asymptomatic and undiagnosed in early life. Additionally, ~3–4% stillbirths and ~10% aborted fetuses have underlying heart defects.

17.5.1 GENERAL CONSIDERATIONS

Incidence of individual CHDs varies with sex and race. Some CHDs are commoner in males (TGA and AS) while others are more common in females (Lt > Rt shunts and PS). VSDs are more common in Asians while TA is common in Whites.

Etiology of CHDs is largely unidentified, considered to be multifactorial:

- ***Familial factors:*** Presence of CHD in a child or parent is associated with higher risk (3–4%) in subsequent children than in general population (<1%). Risk is further increased (10%) in third child, if two siblings (or one parent and one sibling) have CHDs.
- ***Chromosomal/genetic disorders:*** CHDs are common in trisomies, e.g. Down syndrome, Turner syndrome, Marfan syndrome and other genetic disorders. Nearly 85% of conotruncal defects are associated with deletion of a chromosomal segment—22q11.
- ***Environmental factors:*** CHDs are common in babies with intrauterine exposure to—(a) maternal infections, e.g. rubella, (b) maternal illnesses, e.g. diabetes or SLE, and (c) drugs, e.g. phenytoin, warfarin or alcohol.

Table 17.15 lists common cardiac lesions, associated with various genetic defects, intrauterine infections or other risk factors.

Classification: CHDs may be classified clinically as-*(a) acyanotic* or *(b) cyanotic;* or hemodynamically as—*(a) left to right shunts, (b) obstructive lesions* and *(c) right to left shunts* **(Table 17.16)**.

- **Left to right (Lt>Rt) shunts** are commonest CHDs, characterized by an abnormal communication at atrial, ventricular or ductal level, with blood flow

TABLE 17.15: Common CHDs in systemic disorders

Chromosomal/genetic	
Down syndrome	Endocardial cushion defects
Turner syndrome	Coarctation of aorta, AS
Marfan syndrome	AR, mitral valve prolapse
Ehler-Danlos syndrome	MR, mitral valve prolapse
Osteogenesis imperfecta	AR
Intrauterine exposure	
Congenital rubella syndrome	PDA, PS
Maternal Mumps*	Endocardial fibroelastosis
Maternal diabetes	TGA
Hypervitaminosis D*	Supravalvular AS
Maternal SLE*	Heart blocks
Kawasaki disease*	Cardiomyopathy, heart blocks

*Similar lesions may develop even after postnatal exposure.
TGA: Transposition of great arteries.

TABLE 17.16: Classification of CHDs

Acyanotic CHDs
- ***Lt to Rt shunt***
  - Ventricular septal defect (VSD)
  - Atrial septal defect (ASD)
  - Patent ductus arteriosus (PDA)
- ***Obstructive lesions***
  - Pulmonary stenosis (PS)
  - Aortic stenosis (AS)
  - Coarctation of aorta (CoA)

Cyanotic CHDs
- ***Rt to Lt shunts with decreased PBF***
  - Tetralogy of Fallot (ToF)
  - Tricuspid atresia (TA)
  - Ebstein anomaly (EA)
  - Pulmonary atresia (PA)
  - Right hypoplastic heart syndrome (RHHS)
- ***Rt to Lt shunts with increased PBF*****
  - Transposition of great vessels (TGA)
  - Truncus arteriosus (TrA)
  - Total/partial anomalous pulmonary venous return (TAPVC)
  - Single ventricle (SV)
  - Double outlet right ventricle (DORV)
  - Left hypoplastic heart syndrome (LHHS)

PBF: Pulmonary blood flow
**may also present with decreased PBF, if associated with PS.

from high-pressure systemic circuit to low-pressure pulmonary circuit. These CHDs are generally acyanotic (till reversal of shunt or Eisenmengerization) and age of presentation depends on the magnitude of shunt and volume overload on pulmonary circulation due to re-shunting of oxygenated blood back to the lungs.

VSD is the commonest acyanotic CHD with Lt>Rt shunt (~25–30%), followed by ASD (8–10%)* and PDA (6–8%). *ASD is perhaps more common as many cases remain undetected.

- **Obstructive lesions (acyanotic)** are characterized by ventricular (or rarely atrial) outflow obstruction. Each obstructive lesion – PS, AS and CoA, account for ~6–8% of CHDs, though many of them are mild and asymptomatic.

  Unless associated with shunts, these cases usually present in later life with pressure overload and corresponding ventricular failure, i.e. RV failure in PS or LV failure in AS. Obstructive lesions with Rt > Lt communication, present like cyanotic CHDs.
- **Right to left (Rt>Lt) shunts** are cyanotic CHDs, characterized by abnormal communication with blood flow from pulmonary to systemic circuit, leading to mixing of unoxygenated right-sided with oxygenated left-sided blood. Age of the appearance of cyanosis depends on the magnitude of Rt> Lt pressure gradient, anatomical size of shunt and presence/absence of alternative communication to maintain pulmonary flow, e.g. PDA.

Tetralogy of Fallot (TOF) is the commonest cyanotic CHD (5–7%) followed by TGA (3–5%).

Clinical presentation of CHDs is highly variable, depending on the age of onset, type and severity of lesion. Some diseases may remain asymptomatic throughout life while others are lethal *in utero* or present soon after birth. Some important indicators of CHDs are:

- *Presence of murmurs*, due to abnormal blood flow through valves or shunts,
- *Abnormal heart sounds* or signs of the *hypertrophy/dilatation of cardiac chambers*, due to altered pressure gradients between different chambers by shunts or outflow obstruction,
- *Chronic pulmonary congestion*, e.g. recurrent respiratory infections, chest deformities, failure to thrive, etc., indicating increased pulmonary blood flow,
- *Cyanosis, cyanotic spells, clubbing*, etc. Indicating mixing of unoxygenated and oxygenated blood,
- *CCF*, e.g. tachycardia, dependent edema, raised JVP, hepatomegaly, due to failure of compensatory mechanisms.

17.5.2 ACYANOTIC CHDs

Acyanotic CHDs may be broadly divided into two categories – those with volume overload, i.e. *Lt > Rt shunts*, and those with pressure overload, i.e. *obstructive lesions.*

Acyanotic CHDs with volume overload are characterized by Lt > Rt shunt with re-circulation of oxygenated blood back to the lungs. Magnitude of shunt depends on the size of defect and pressure gradient between pulmonary and systemic circuits. As these factors are dynamic, pathophysiology and clinical picture may change with age, as follows:

- Since pulmonary vascular resistance is high at birth due to poorly expanded lungs, Lt > Rt shunt is minimum in newborns with no murmurs. Murmurs generally appear after a few days, as pulmonary arterial pressure drops below the systemic pressure.

- In large shunts, increased inflow on right side via Lt > Rt shunts may lead to right sided volume overload and increased pulmonary blood flow, which manifests with ill-sustained sucking, recurrent chest infections or frank CCF.
- Persistent elevation of pulmonary blood flow may produce secondary changes in pulmonary vasculature, leading to development of pulmonary arterial hypertension (PAH). Over the years, rising pulmonary pressure may equalize and then exceed the systemic pressure, leading to reversal of shunt-flow, i.e. *Eisenmengerization* with appearance of cyanosis.

Acyanotic CHDs with pressure overload are obstructive lesions, characterized by ventricular outflow obstruction (AS, PS, CoA) and clinical presentation depends on magnitude of obstruction.

Some common acyanotic heart diseases have been discussed in this section.

1. Ventricular Septal Defect (VSD)

VSD is the commonest cardiac malformation, accounting for ~25% of CHDs. It is also an integral part of many cyanotic CHDs, though present section deals with only isolated defects.

Anatomically, 90% of VSDs are located in the membranous portion of interventricular septum *(membranous VSDs)*, while rests are in muscular part (*muscular VSDs*). Size-wise, VSDs may be classified as *small or restrictive* (<0.5 cm^2), *moderate* (0.5–1.0 cm^2) or *large* (>1.0 cm^2). VSDs with inter-ventricular pressure gradient of >64 mm Hg are also termed restrictive VSDs.

Hemodynamics and consequent clinical presentation in VSD depend on its size and magnitude of shunt across the ventricles, as discussed below and graphically presented in **Fig. 17.14**.

- Primary hemodynamic defect in VSD is a trans-septal *LV > RV shunt* due to higher pressure in LV (100/70 mm Hg) than in RV (30/10 mm Hg). Since this pressure gradient persists throughout the systole, typical murmur is pansystolic *(PSM)* in left parasternal area (3–4th space), which is *louder in smaller VSDs* (due to higher flow turbulence across a smaller gap). At birth, shunt is minimal due to higher pulmonary resistance/RV pressure and murmur is absent, which usually appears by the end of first week due to gradual drop in pulmonary resistance after expansion of lungs and consequent increase in shunt flow.
- Increased RV volume due to trans-VSD flow, leads to—(a) *CCF* after variable time-gap, (b) ESM in pulmonary area due to increased pulmonary blood flow, and (c) *loud/palpable* P_2 due to secondary PAH. However, *RVH is uncommon* despite PAH, as systolic shunt-flow in VSD is mainly directed towards the pulmonary valve, when RV is also contracting.

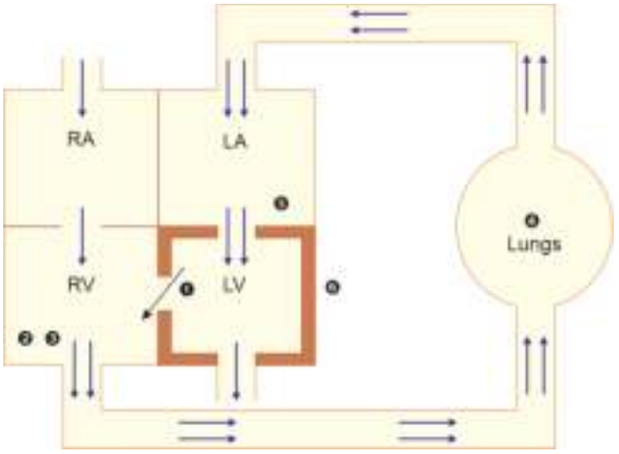


Fig. 17.14: Hemodynamics: VSD.
(1) VSD; (2) RV Volume overload; (3) PAH; (4) ↑PBF; (5) ↑Flow across mitral valve, (6) LVH. *Double arrows indicate extra blood flow.*

- Increased pulmonary blood flow leads to pulmonary congestion with feeding difficulties, recurrent chest infections and pulmonary plethora on chest skiagram.
- Increased pulmonary blood flow also enhances venous return to LA and flow across the mitral valve, producing a *late or mid diastolic murmur,* due to increased flow across a normal-size valve (*functional MS*).
- Increased in-flow in LV from LA as well as the need for stronger contractions to maintain adequate cardiac output in view of LV>RV leak, leads to *LV volume overload and LVH* respectively with hyperdynamic apex-beat, shifted downwards and outwards.
- Early closure of aortic valve due to LV leak through VSD and late closure of pulmonary valve due to additional blood volume in RV via shunt, leads to *wide splitting of second HS*.

In small VSDs, pathology is usually limited to a small shunt (loud murmur) without significant hemodynamic changes.

Clinical manifestations depend on the size of the defect. While small VSDs may remain asymptomatic in childhood and diagnosed accidentally, large VSDs may present even in neonatal period. Most cases present by 6–10 weeks, with symptoms suggestive of *increased pulmonary blood flow*, e.g. feeding difficulties (suck-rest-suck cycle) and recurrent chest infections. Important clinical signs are given in **Table 17.17**.

Size of the VSD may be clinically assessed by—(a) age of presentation, (b) magnitude of symptoms, (c) loudness of PSM, (d) loudness of P_2, and (e) severity of PAH. Asymptomatic/late-manifesting VSD with loud PSM *but* without loud P_2 or significant PAH indicates small VSD.

Diagnosis depends on:

- *Chest X-ray* suggestive of LVH with pulmonary plethora.

TABLE 17.17: Important signs in VSD	
Peripheral	CCF, failure to thrive
Central	
Inspection	Pre-cordial bulge
Palpation	Lateral-downward apex beat (LVH) Palpable P_2 Systolic thrill at left parasternal area
Auscultation	Loud S_2, may be split PSM at left parasternal area* ESM at pulmonary area DM/LDM at mitral area
Chest X-ray	LVH/BVH with pulmonary plethora
ECG	LVH/BVH

*characteristic clinical sign

- *ECG* suggestive of LVH or biventricular hypertrophy.
- *Echocardiography* with Doppler studies is essential to—(a) visualize position/size of VSD, (b) estimate shunt-size by assessing the volume overload in LV/LA and (c) assess severity of PAH.
- *Cardiac catheterization* is required before surgery to identify exact hemodynamic status.

Course and complications: Natural course depends on the size of VSD and includes:

- *Spontaneous closure* by 2–3 years in 30–50% cases, though remaining VSDs may also reduce in size. Small, muscular VSDs are more likely to close than large and membranous VSDs. Spontaneous closure after 3 years of age is unlikely (<10%).
- *Recurrent CCF,* usually by 2–3 months in large VSDs and by late infancy in moderate defects.
- *Infective endocarditis* is more common in small VSDs, due to small but more forceful shunt flow causing jet injury on RV walls.
- *Development of subvalvular PS,* due to hypertrophy of RV infundibulum in ~10% cases, which may increase RV pressure with reduce shunt flow and symptomatic improvement.
- *Development of pulmonary vascular obstructive disease* following long-standing hyperdynamic pulmonary hypertension in moderate/large defects.
- *Aortic valve prolapse* with aortic regurgitation, specially in supracristal VSDs due to loss of support to the coronary cusp.
- *Eisenmengerization,* i.e. reversal of shunt in large VSDs or those with associated PS, due to gradual rise in RV pressure and reversal of pressure-gradient across the ventricles. Clinically, these cases may show temporary symptomatic improvement with disappearance of murmur due to reduction in Rt>Lt shunt before appearance of cyanosis due to reversed Lt>Rt shunt.

Management involves closure of the defect by open surgery (*Patch closure*) or interventional device closure, as follows:

- Large VSDs with refractory CCF or severe PH must be operated as early as possible, while those with controlled CCF must be operated by 6 months.
- Moderate size VSDs should be operated by 1–2 years, if controlled by medications. However in asymptomatic cases, surgery is generally deferred till 2–5 years of age in expectation of the spontaneous closure.
- Surgery is not indicated in small VSDs (<3 mm) unless they develop aortic valve prolapse, progressive RV outflow obstruction or Infective endocarditis.
- All VSDs, irrespective of the size or severity, should be operated as soon as possible in case of aortic cusp prolapse or significant aortic regurgitation.
- Surgery is contraindicated in cases with severe PH or irreversible pulmonary vascular disease and may be difficult in multiple or inaccessible VSDs, who may benefit by pulmonary artery bending procedures.
- *Device closure* is preferred in cases weighing >8 kg with adequate rim around the defect including—(a) mid-and anterior-muscular VSDs, (b) post-operative residual VSD, and (c) perimembranous VSDs at least 4 mm away from aortic valve. Device closure is contraindicated in cases with associated AR, conduction abnormalities, who should be treated surgically.
- After device closure, patient has to be on follow-up with anti-platelet therapy and infective endocarditis prophylaxis for 6 months. IE prophylaxis is also indicated after surgery.
- Operative mortality is <2% and complications include heart block and re-opening of defect.

Medical management till surgery includes: (a) regular follow-up, (b) early management of CCF, infections, anemia, etc., and (c) infective endocarditis prophylaxis.

2. Patent Ductus Arteriosus (PDA)

Patent ductus arteriosus (PDA) denotes persistence of *fetal communication between left pulmonary artery and descending aorta*, distal to the origin of left subclavian artery. Normally, this communication (*ductus arteriosus*) closes functionally within 10–12 hours of birth and anatomically by 4–6 weeks (*Ligmanetum arteriosum*).

Isolated PDA accounts for ~6–8% of CHDs. In addition, PDA is also present as life-saving component in many obstructive and cyanotic CHDs, offering alternative route for pulmonary blood flow.

PDA is three times more *common in females* than in males. It is also frequently present in extreme preterms and closes spontaneously with maturity, indicating merely a developmental delay. In term newborns, it is a structural defect in the muscular wall, unlikely to close spontaneously or by medical therapy.

Hemodynamics and consequent presentation in PDA depends on the magnitude of shunt, as discussed below and graphically presented in **Fig. 17.15**.

- Primary hemodynamic defect in PDA is trans-ductal Lt > Rt shunt, due to higher pressures in descending aorta (120/80 mm Hg) than in left PA (25/05 mm Hg). As this pressure gradient persists during systole as well as diastole, PDA murmur is typically a *continuous machinery murmur in left infraclavicular region*, more marked in systole.
- The shunt is minimal at birth due to high PA pressure and *PDA murmur generally appears after 24–48 hours*, corresponding to gradual expansion of lungs and fall in PA pressure. In presence of significant PAH, murmur may only be systolic due to equalization of aortic and pulmonary pressure in diastole.
- Increased pulmonary blood flow due to extra-flow received via ductus, leads to pulmonary congestion with *recurrent respiratory infections and feeding difficulties;* and subsequently development of PAH with *loud P_2 and ESM at pulmonary area.*
- *Increased venous return* from congested lungs leads to LA volume overload and dilatation.
- Increased LA volume increases flow across the mitral valve to produce *loud S_1, delayed diastolic murmur at apex and occasionally, the S_3*. Intensity of S_1 and this murmur correlates directly with severity of shunt.
- Increased flow from LA as well as the need for stronger LV contractions to maintain adequate systemic circulation (in view of leak form aortic side at ductus) leads to LV volume overload and *LVH* respectively, presenting with *hyperdynamic apex beat, shifted downwards and outwards*.
- LV volume overload increases LV emptying time, leading to *delayed A_2 with narrow, absent or reverse (paradoxical) split of S_2*. Increased LV outflow though a normal size aortic valve may also produce an *ESM at aortic area* as well as an *ejection click* due to dilatation of aortic root. However, this ESM is generally drowned in continuous murmur.
- Leak from aortic side via ductus leads to rapid drop in aortic pressure during ventricular diastolic phase, with *water-hammer pulse* and *wide pulse pressure*.

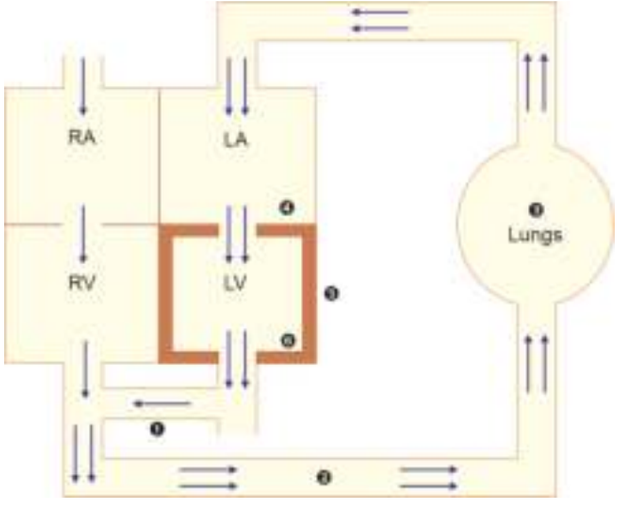


Fig. 17.15: Hemodynamics: Patent ductus arteriosus.
1. PDA; 2. PAH; 3. ↑PBF, 4. ↑Flow across mitral valve, 5. LVH, 6. ↑LV outflow. *Double arrows indicate extra blood flow*.

Clinical manifestations depend on the magnitude of shunt and very small PDA may remain asymptomatic or manifest in late childhood. Most cases present at 6–10 weeks with symptoms suggestive of increased pulmonary blood flow, e.g. feeding difficulties (suck-rest-suck cycle), recurrent chest infections, failure to thrive or frank CCF. Important clinical signs are given in **Table 17.18**.

Diagnosis depends on:

- *Chest X-ray* suggestive of LVH with pulmonary plethora. Aortic knuckle may be prominent due to dilatation of the aortic root.
- ECG suggestive of LVH with/without strain pattern (deep Q and tall T waves in left chest leads).
- Echocardiography helps to visualize the shunt and assess ventricular sizes and pressures.

Course and complications: *Spontaneous closure* is possible in preterms and may be hastened by indomethacin therapy. Organic PDA does not close spontaneously or by medical therapy and can lead to:

- *CCF* at any age after first 24–48 hours,
- *Infective endocarditis* with vegetations on pulmonary side of shunt
- *Rarely, Eisenmengerization* due to severe PAH. In *Eisenmengerization* of PDA, cyanosis is typically *differential*-more prominent in lower limbs due to ductal mixing beyond the left subclavian artery.

TABLE 17.18: Important signs in PDA

Peripheral	:	CCF, failure to thrive Wide pulse pressure*
Central		
Inspection	:	Pre-cordial bulge
Palpation	:	Lateral-downward apex beat (LVH)
		Infraclavicular continuous thrill
Auscultation	:	Loud S_1
		Absent/reverse splitting of S_2
		Infraclavicular continuous murmur*
		LDM at mitral area
		Ejection click and ESM at aortic area
		Loud P_2 and ESM at pulmonary area
Chest X-ray	:	LVH with pulmonary plethora
ECG	:	LVH

*characteristic clinical signs

Management may be divided into:

- ***Supportive therapy*** with adequate nutrition, early diagnosis/treatment of CCF and chest infections, regular follow-up and prevention of infective endocarditis.
- ***Medical closure*** is possible only in preterms, by IV/PO Indomethacin, a prostaglandin synthetase inhibitor (0.1 mg/kg/dose), given as three doses at 12-hourly intervals. It is *contraindicated* in babies with hepatic/renal disease, bleeding tendencies or ductus-dependent cyanotic lesions. Ibuprofen (PO, three doses as 10 mg/kg >5 mg/kg >5 mg/kg at 12-hr intervals) may also be used.
- ***Surgical closure*** is indicated in all cases including failed medical closure in preterms, either by open surgical ligation or preferably by transcatheter devices as follows:
  - Closure is recommended by 3 months in large PDAs or moderate PDAs with CCF, 6–12 months in moderate PDAs without CCF and 12–18 months in smaller defects.
  - Closure intervention is contraindicated in cases with irreversible pulmonary vascular disease.
  - Device closure is preferred in babies weighing >6 kg while surgical ligation is advisable in lighter cases or those with unusual PDA shape, progressive/symptomatic aneurysm or endarteritis. Operative mortality is <1%.
  - Infective endocarditis prophylaxis is indicated during next 6 months.

3. Atrial Septal Defects (ASD)

Isolated ASDs account for ~8–10% of CHDs, twice more *common in females.* In addition, ASD is frequently present in various cyanotic CHDs. Exact incidence may be much higher, as many ASDs remain undetected throughout the life.

Patent foramen ovale (PFO) is a common echocardiographic finding, usually of no hemodynamic significance and is not considered as ASD. However, PFO may play an important role if other structural heart defects are present. It also provides a route for paradoxical systemic embolization.

Anatomically ASD may be divided into:

- Common ***Ostium secundum (OS) defects*** (70–80%), at the site of fossa ovalis. In practice, the term ASD is used *only* to denote these defects, discussed here.
- Uncommon ***Ostium primum defects*** (15–20%) or endocardial cushion defects in lower atrial septum below the fossa ovalis, frequently associated with clefts in mitral or tricuspid valve leaflets.
- Rare ***sinus venosus defects*** (5–10%) located in postero-superior septum at the site of superior vena caval entry into RA.

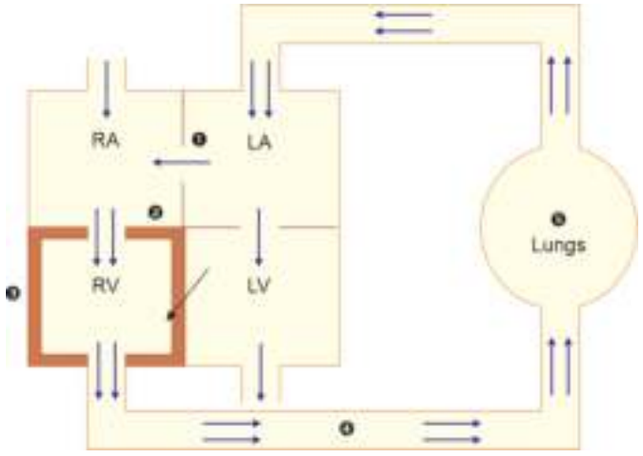


Fig. 17.16: Hemodynamics: Atrial septal defect

1. ASD; 2. RA Volume overload; 3. RVH; 4. PAH; 5. ↑PBF

Note: 3, 4. and 5. develop after many years. *Double arrows indicate extra blood flow*.

Hemodynamics in common OS-ASD depend on the size of defect and relates more to the volume changes in atria rather than pressure changes, due to relatively compliant and less muscular atrial chambers. Most cases do not manifest till second decade, unless having very large defects. Important hemodynamic changes are discussed here as well as graphically presented in **Fig. 17.16**.

- Primary hemodynamic defect in OS-ASD is Lt > Rt shunt at the atrial level, which is usually minimal and silent due to nearly comparable pressures in atria (0–5 mm).
- In large defects, significant shunt leads to RA volume overload and dilatation (*tall peaked P waves in* V_{1-2} on ECG) as well as increased flow across the tricuspid valve, producing *late diastolic rumbling murmur at tricuspid area.*
- Increased flow into RV produces volume overload and some RVH on X-ray/ECG, but less obvious clinically.
- RV volume overload increases flow across the pulmonary valve, producing *ESM at pulmonary area, delayed* P_2 *and consequently splitting of second HS*. As RV is already overloaded, further increase in RV volume during inspiration, as seen normally, is not possible, leading to *fixed split of* S_2.
- After many years, usually in second decade, RV volume overload may lead to CCF and/or increased pulmonary blood flow, with onset of clinical manifestations.

Clinical manifestations: Isolated ASD is usually asymptomatic in childhood, diagnosed accidentally. Most cases manifest in late adolescence or early adulthood with features of increased pulmonary blood flow, e.g. effort intolerance or recurrent chest infections. Important clinical signs are given in **Table 17.19**.

TABLE 17.19: Important signs in ASD

Peripheral	:	Usually nil
Central		
Inspection	:	Nil
Palpation	:	Lateral shift of apex beat (RVH) +/–
		Parasternal heave (RVH) +/–
		Ejection systolic thrill at pulmonary area +/-
Auscultation	:	**Wide and fixed split of S_2***
		ESM at pulmonary area
		LDM at tricuspid area
Chest X-ray	:	RVH/normal
ECG	:	RVH, rsR' pattern

*characteristic feature, may be the only sign

Diagnosis is supported by:

- *Chest X-ray* suggestive of RVH with normal pulmonary blood flow. Sometimes, pulmonary conus may be prominent due to pulmonary artery dilatation. Pulmonary blood flow may be minimally increased in large defects or older children.
- *ECG* showing RVH with right-axis deviation and rsR' pattern (pathognomonic in ~90%) in right chest leads suggestive of right bundle branch block.
- *Echocardiography* reveals—(a) exact location and size of the defect in subcostal 4-chamber view, (b) abnormalities in RA, RV and PA size, (c) paradoxical motion of intra-atrial septum on M-mode. Doppler studies reveal characteristic flow pattern with maximum shunt during diastole.

Course and complications: Nearly all ASDs <3 mm close spontaneously by 2 years, while those >8 mm are unlikely to close. Complications, e.g. CCF or PAH are rare before third decade, *except* arrhythmias, e.g. sick sinus syndrome. Infective endocarditis is very rare in isolated ASD and prophylaxis is not required.

Management involves surgical or device closure, as follows:

- All asymptomatic ASDs should be operated at 2–4 years of age, except that the surgery in sinus venosus defects may be delayed till 4–5 year. ASDs diagnosed later than recommended age for surgery should be operated soon after the diagnosis.
- Earlier closure is recommended in symptomatic ASDs with CCF and PH, after ruling out associated cardiac defects.
- Surgery is contraindicated in rare cases with severe PH or irreversible pulmonary vascular disease.
- Device closure is preferred for OS-ASD with good rim ≥ 5 mm, while others may need surgical repair with operative mortality of < 1%.
- After device closure, patient has to be on follow-up with anti-platelet therapy and infective endocarditis prophylaxis for 6 months. IE prophylaxis is also indicated after surgery.

4. Aortic Stenosis (AS)

Aortic stenosis (AS) may be congenital or rheumatic, though later is extremely rare in childhood. Congenital AS accounts for 5–8% of CHDs, more common in males.

Structurally, congenital AS may be valvular, supravalvular or subvalvular in location.

- *Valvular AS due to bicuspid aortic valve is the commonest CHD in adults*, present in ~2% population.
- *Subvalvular stenosis* is usually seen with other CHDs or hypertrophic cardiomyopathy.
- *Supravalvular stenosis* is seen in *William syndrome* — with Elfin-facies, mental retardation and idiopathic hypocalcemia.

Clinical presentation depends on the site and severity of LV outflow obstruction. While mild cases are usually asymptomatic, severe AS present with easy fatigability and syncopal attacks, due to lower cardiac output. Important signs include:

- *Low-volume pulse* and *narrow pulse pressure* due to reduced LV output,
- A diamond-shaped, *ejection systolic murmur* in right second intercostal space due to LV outlet obstruction, which is typically referred to the neck,
- An *ejection click* just before the ESM, due to post-stenotic dilatation of ascending aorta in valvular lesions.
- *Heaving apex beat, displaced downward and laterally* due to systolic LV overload and LVH
- *Narrow or reverse splitting of S_2*, due to increased LV ejection time > delayed AV closure.

Diagnosis is supported by—(a) chest skiagram showing LVH with dilatation of aortic knuckle, (b) ECG suggestive of LVH, and confirmed on (c) echocardiography.

Management: Asymptomatic mild AS need no intervention except avoiding strenuous exercise, which may precipitate hemodynamic decompensation.

Symptomatic cases need either—(a) balloon aortic valvuloplasty for valvular/subvalvular lesions, (b) surgical valvotomy or (c) valve replacement, as follows:

- *Valvular or supravalvular AS* needs immediate surgery/balloon dilatation in newborns with critical AS or severe LV dysfunction, while elective balloon dilatation is indicated in cases with peak gradient >64 mm Hg, mean gradient >40 mm Hg, symptomatic AS or ST changes on ECG even with lower gradients.
- Subvalvular AS needs surgery if (a) peak gradient is 50 mm Hg *or* (b) peak gradient is <50 mm Hg but with associated moderate to severe AR or LV dysfunction *or* (c) plans to involve in competitive sports
- Infective endocarditis prophylaxis is indicated for next 6 months after valvuloplasty or life-long in cases of prosthetic valve replacement.

5. Pulmonary Stenosis (PS)

Pulmonary stenosis (PS) may be an isolated defect or a component of other CHDs. It is the commonest CHD in *Noonan syndrome*.

Structurally, It may be *valvular* (commonest), *supravalvular* or *infundibular* (subvalvular). Co-existing hypoplasia/stenosis of distal pulmonary vessels is common and needs to be excluded before surgery.

Clinical presentation depends on the severity of RV outflow obstruction. While mild cases are usually asymptomatic, moderate to severe PS presents with CCF at variable age. Important signs include:

- A *diamond shaped ESM* in pulmonary area, due to outflow obstruction,
- Soft or absent P_2 in valvular PS, though it may be louder in supravalvular PS.
- *Wide splitting of* S_2 due to-prolonged RV ejection time > delayed PV closure.
- An *ejection click* in pulmonary area indicates valvular PS with post-stenotic dilatation of PA.
- *Lateral shifting of apex beat* and left parasternal heave, due to RVH.

Diagnosis is supported by—(a) chest X-ray showing RVH, oligemic lung fields and absence or post-stenotic dilatation of pulmonary conus, (b) ECG suggestive of RVH, and (c) chocardiography to assess the severity.

Treatment of choice is the *Balloon dilatation with/without stenting*, alternative being surgery with/without valve replacement, as follows:

- *All cases* needs immediate intervention in newborns with critical PS or severe LV dysfunction, while elective balloon dilatation is indicated in cases with—(a) peak gradient >64 mm Hg, (b) mild RV hypoplasia causing hypoxia or (c) dysplastic pulmonary valve.
- All cases of peripheral PA or branch stenosis with—(a) >50% diameter narrowing, (b) RV systolic pressure >50 mm Hg, or (c) >20% difference in perfusion of both lungs on perfusion scan also need balloon dilatation with/without stenting or surgery.
- Infective endocarditis prophylaxis is indicated for next 6 months after valvuloplasty or life-long in cases of prosthetic valve replacement.

6. Coarctation of Aorta (COA)

Coarctation of aorta (CoA), i.e. *localised or diffuse narrowing of aorta from any point between transverse arch to iliac bifurcation*, contributes to ~2–3% of CHDs in children. CoA is twice more common in males, sometimes associated with *Turner* or *Noonan* syndrome.

Over 70% CoA also have VSD *or* left-sided lesions, e.g. bicuspid aortic valve, mitral valve abnormalities, etc., together referred as *Shone complex*.

Anatomically, all CoA may be broadly divided into two types, with significant differences in hemodynamics and clinical presentations:

a. *Juxtaductal CoA* accounts for ~98% CoA, characterized by coarctation *at the level* of ductus arteriosus, just below the origin of left subclavian artery.
b. *Pre-ductal or infantile CoA* (<2%), characterized by localized coarctation or diffuse tubular hypoplasia *before* the ductus arteriosus.

Hemodynamically two facts are worth considerations:

a. Upper half of the body is supplied by preductal branches of ascending/transverse aorta (innominate, left carotid/subclavian), while lower body is supplied by post-ductal branches of descending aorta. In CoA, deficient flow in descending aorta leads to development of:
   - Pulse-BP deficit between upper and lower body,
   - Renal ischemia and consequent hypertension, and
   - Collaterals between preductal and postductal vessels to augment distal blood flow.
b. *In utero*, upper body receives more oxygenated preductal flow from LV, while distal body is largely supplied by less oxygenated blood through RV > PDA > descending aorta.
   - *In juxtaductal CoA*, coarcted segment interferes with ductal flow, leading to development of collaterals in fetal life itself, which partially sustain the distal flow after postnatal ductal closure. Hence, most cases manifest in later life with hypertension **(Fig. 17.17)**.
   - *In preductal CoA*, coarcted segment does not obstruct the ductal flow and hence, collaterals do not develop in fetal life. Absence of collaterals at the time of birth and postnatal ductal closure in these cases leads to—(a) sudden drop in descending aortic pressure, with hypertension, and (b) sudden increase in proximal aortic pressure with LVH.

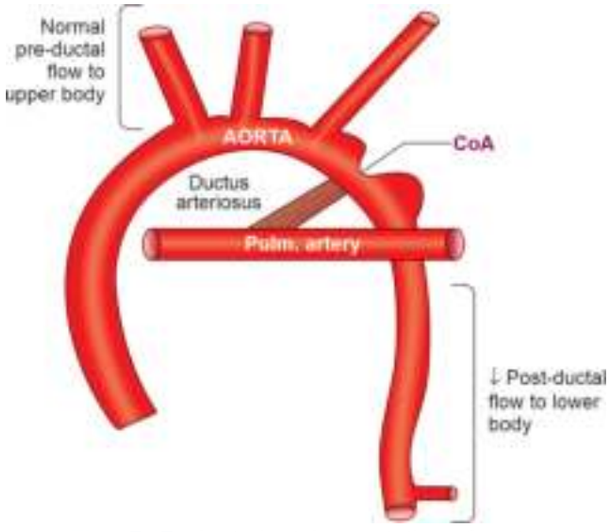


Fig. 17.17: Juxtaductal coarctation of aorta.

Consequently, most cases or preductal CoA present with severe hypertension, LVH and CCF in neonatal period or early infancy. In some cases, low aortic pressure in post-coarcted segment or severe pulmonary arterial hypertension may facilitate longer patency of PDA with Rt > Lt shunt, leading to *differential cyanosis* in lower limbs.

Hemodynamic changes in CoA are further altered by presence of co-existing heart lesions, e.g. VSD.

Clinical spectrum of CoA varies according to the severity and location of defect, as well as presence of coexisting cardiac lesions.

Uncomplicated Juxtaductal CoA, usually presents with asymptomatic or symptomatic hypertension in late childhood, though some cases may complain of weakness and leg pains after exercise (? due to ischemia).

Important clinical signs include:

- *Systolic hypertension*, more prominent on exercise.
- *Pulse/BP disparity* between upper and lower limbs, more prominent on exercise and presents with:
  - *Absent/poor pulsations in lower limb* vessels, e.g. femoral, popliteal or dorsalis pedis artery;
  - *Radiofemoral delay*, due to slower filling of descending aorta by collaterals rather than by direct aortic flow,
  - *Less BP in lower limbs* than upper limbs (normally, lower limb BP exceeds upper limb BP by 10–20 mm Hg). Lower BP in left arm than in right arm suggests involvement of left subclavian artery in coarcted segment.
- Long systolic or continuous murmurs over chest and back due to collaterals.
- Cardiac signs depend on severity of obstruction and co-existing heart lesions, ranging from normal precordium to:
  - Signs of aortic flow obstruction, e.g. prominent arterial pulsations in neck and/or ejection systolic murmur in interscapular area.
  - Signs of LV overload, e.g. loud A_2, ejection click or LVH (down/outward heaving apex beat).
  - Signs of other heart lesions, e.g. aortic ESM/ LDM (bicuspid aortic valve), mitral MDM (MS), etc.

Preductal CoA presents in neonatal period with cyanosis/differential cyanosis and CCF, though some cases have delayed presentation after the closure of ductus. Pulse/BP disparity is less prominent in these cases and collateral murmurs are rare.

Complications: CCF is the most important complication of CoA in infancy, in cases with preductal/severe juxtaductal disease or co-existing heart lesions. Untreated cases of moderate/mild CoA are usually asymptomatic in childhood except potential risk of infective endocarditis with vegetations on aortic wall or bicuspid aortic valve.

Most cases develop hypertensive complications in 2nd–3rd decade, e.g. (a) CCF, (b) hypertensive encephalopathy, (c) premature coronary disease, (d) aortic aneurysms. Cerebrovascular accidents are common in cases with coexisting intracranial aneurysms, e.g. Berry's aneurysm.

Diagnosis is clinically indicated by hypertension with pulse-BP deficit and supported by:

- *Chest X-ray* may be normal in early life. Late signs include—(i) mild LV cardiomegaly, (ii) prominent aortic knuckle, (iii) pre-/post-stenotic dilatation of aorta, and (iv) notching of the lower rib borders due to collaterals.
- *Barium swallow* may reveal characteristic *E sign*, due to pre-and post-stenotic dilatation.
- *ECG* may be normal or reveals LVH.
- *Echocardiography*, for—(i) direct visualization of coarctation through suprasternal approach, (ii) detection of co-existing heart lesions.
- *Color Doppler studies* to assess the—(i) severity of coarctation by recording pre-stenotic *vs* post-stenotic pressure gradient, (ii) status of collaterals.
- *Cardiac catheterization* to detect additional heart defects and adequacy of collateral flow, before surgery in established case.

Management of CoA is essentially surgical, after stabilization with supportive medical treatment, e.g. treatment of CCF. Infants with *pre-ductal or severe juxtaductal CoA* are usually ductus-dependent and may require prostaglandin E_1 infusions to re-open or keep the ductus patent till surgery is arranged. Important principles of surgical management include:

- All cases of CoA with peak gradient 20 mm Hg, LV dysfunction or LVH, hypertension or >50% narrowing relative to aortic diameter at diaphragm on imaging studies need intervention
- Cases with significant LV dysfunction, CCF or severe hypertension should be operated immediately, while others must be operated as soon as possible, i.e. between 3 months to 2 years. Surgical risk increases with advancing age due to deteriorating LV function and degenerative changes in aortic wall.
- Balloon angioplasty is generally preferred over surgical aortoplasty due to less operative morbidity, mortality and costs, though carries higher risk of aneurysm formation. Surgical aortoplasty is necessary in newborns with aortic arch hypoplasia.

  Children > 25 kg or those with post-operative re-coarctation may need stenting, which is contraindicated < 10 years of age.
- Important *post-operative complications* include—(a) transient rebound hypertension in immediate post-operative period, and (b) late re-coarctation, specially in cases operated in infancy. Infective endocarditis prophylaxis is indicated for next 6 months.

17.5.3 CYANOTIC CHDs

Cyanotic CHDs (Rt > Lt shunts) may be broadly divided into two categories—(a) those with decreased pulmonary blood flow (PBF), and (b) those with increased PBF.

Cyanotic CHDs with decreased PBF essentially have two lesions—an obstruction to PBF at tricuspid or pulmonary valve level (usually PS), and a Rt > Lt shunt at atrial or ventricular level. Common lesions of this group include tetralogy of Fallot (TOF), tricuspid atresia, pulmonary atresia, and total anomalous venous drainage (TAPVR) with PS.

Severity of cyanosis in these cases depends on the degree of PBF obstruction and status of ductus arteriosus that provides alternate route to PBF. These newborns are usually not-cyanotic during first few days of life due to ductal patency and cyanosis appears as the ductus closes.

Cyanotic CHDs with increased PBF are characterized by Rt > Lt shunt *but* without PBF obstruction (no PS). In these cases, severity of cyanosis depends on the size of shunt and most cases present with a combination of cyanosis and CCF. Common lesions in this group include transposition of great arteries (TGA), truncus arteriosus, single ventricle, or TAPVR without PS.

Apart from cyanosis and CCF, other common complications of cyanotic CHDs include:

- *Compensatory polycythemia,* leading to thromboembolic complications and Iron deficiency anemia,
- *Metabolic complications* due to hypoxic tissue injury and increased cell mass, e.g. (i) hyperuricemia and *gout*, (ii) hyperkalemia, (iii) hyperphosphatemia, (iv) hypocalcaemia (secondary to hyperphosphatemia), etc.

Some common cyanotic CHDs are as follows:

1. Tetralogy of Fallot (TOF)

Tetralogy of Fallot (TOF) is the commonest cyanotic CHD, accounting for >8–10% of all CHDs.

Anatomically it is characterized by four components-two primary lesions: (a) *pulmonary stenosis*, usually of infundibular type, and (b) *ventricular septal defect,* usually peri-membranous; as well as two secondary lesions, (c) *overriding of the aorta,* receiving blood from both ventricles, and (d) *right ventricular hypertrophy*.

Associated defects include hypoplasia of pulmonary or coronary vessels, PDA or right-sided aortic arch.

Fallot physiology is a term used to describe certain cyanotic CHDs with decreased PBF and ToF-like clinical presentation, ECG and X-ray abnormalities, e.g. (a) TGA with VSD and PS, (b) double outlet right ventricle (DORV) with VSD and PS, (c) single ventricle with PS, (d) tricuspid atresia with diminished PBF. Echocardiography is essential to distinguish between these disorders.

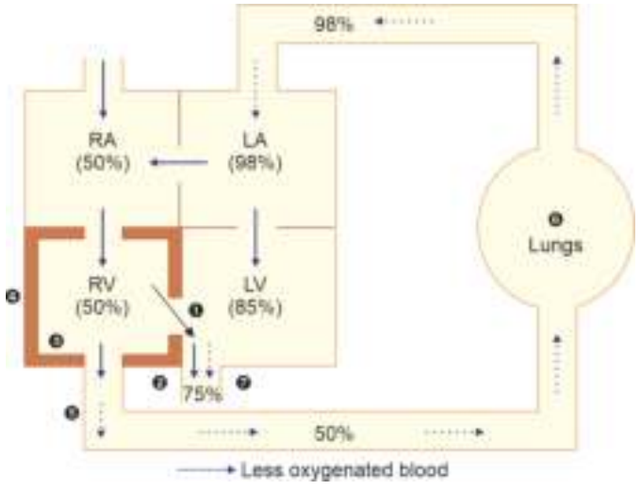


Fig. 17.18: Hemodynamics: Tetralogy of Fallot
1. VSD; 2. Overriding aorta; 3. PS; 4. RVH; 5. ↓ PBF; 6. Olegimic lungs; 7. Mixing at aortic level.

Hemodynamics: Severity of TOF primarily depends on the severity of PS and extent of aortic overriding. Important hemodynamic changes in TOF are discussed below and presented in **Fig. 17.18**.

- PS is the most critical determinant of severity in ToF, presenting with *absent P_2 and ESM at PA.* Although intensity of ESM increases with increasing severity of PS, it may be very soft in tight PS.
- RV outflow obstruction due to PS leads to—(a) increased RV pressure and (b) decreased PBF. However since RV has sufficiently large outlet through VSD and overriding aorta, *CCF is rare* in TOF despite PS.
- Increased RV pressure leads to Rt > Lt shunt through VSD. However, due to perimembranous location of VSD and overriding aorta, most of the shunt-flow enters directly into aorta and *mixing of oxygenated and unoxygenated blood occurs at aortic level and not in the left ventricle.* Magnitude of shunt at aortic level (and consequently the severity of cyanosis) depends on the extent of aortic overriding and RV pressure. An *ejection click* may be audible at aortic area due to dilatation of aortic root in some cases. *Rt > Lt shunt at ventricular level via VSD is usually insignificant and silent*, except in severe PS, due to lack of significant pressure gradient between two ventricles.
- Decreased PBF further contributes to cyanosis. However, in newborns or older cases with PDA, PBF may be maintained via Lt > Rt shunt at ductal level. In long-standing cases, major aortopulmonary collateral arteries (MAPCAs) may develop to augment PBF, producing *functional flow murmurs* over chest and back.

Clinical manifestations of TOF include:

- ***Cyanosis:*** Age of the appearance of cyanosis and its severity depends on the severity of PS. Most cases manifest by 8–12 weeks of life. *Cyanosis is never present*

at birth in TOF as relatively patent ductus during first few days of life allows enough flow to reach pulmonary circulation. Children with mild PS have insignificant Rt > Lt shunt and cyanosis may absent (*Pink Fallot*).

- ***Cyanotic or anoxic spells:*** Cyanotic spells are characterized by sudden, paroxysmal worsening of basal cyanosis with dyspnea, altered sensorium and occasionally seizures, lasting for few minutes. Exact etiology of these spells is unclear, probably relates to sudden and unexplained subpulmonic infundibular spasms, further diminishing the PBF. These attacks may occur at rest or in crying child with variable frequency, i.e. a few to multiple attacks every day. Cyanotic spells are more common <2 years of age and in anemic children.
- ***Squatting position:*** These children develop a preference for squatting or curled-up position by late infancy, as an adoptive mechanism to reduce systemic venous return (RV pressure) and increase systemic vascular resistance (LV pressure), thus reducing the Rt > Lt shunt.
- ***Clubbing:*** Although exact pathogenesis is unclear, chronic nail-bed hypoxia in cyanotic CHDs leads to dilatation of underlying capillaries, opening up of alternate AV fistulas, interstitial edema and reactive tissue hypertrophy, all leading to clubbing.
- ***Dyspnea*** of variable severity with effort intolerance or feeding difficulties is often the first manifestation, even before appearance of cyanosis.
- ***Growth retardation*** *and failure to thrive,* due to reduced oxygen supply and higher metabolic requirements is common.

Important signs in TOF are summarized in **Table 17.20**.

Complications include:

- *Thromboembolic* complications, due to compensatory polycythemia, e.g. (a) cerebral thrombosis, and (b) cerebral abscesses. *Cerebral thrombosis* is common < 2 years of age, while *cerebral abscess* is common in older children. Clinically, these cases present like cerebrovascular strokes.
- *Iron deficiency anemia*, due to compensatory polycythemia,
- *Metabolic* complications, due to increased cell mass (polycythemia) coupled with hypoxic tissue injury, e.g. (i) xanthinuria and *gout*, (ii) hyperkalemia, (iii) hyperphosphatemia, (iv) hypocalcemia due to hyperphosphatemia, etc.

Infective endocarditis and CCF are rare in TOF.

Table 17.20: Important signs in TOF

Peripheral	Cyanosis*, clubbing, growth failure
Central	
Inspection	Lateral shift of apex beat (RVH)*
Palpation	Left parasternal heave (RVH)
Auscultation	ESM at pulmonary area due to PS*
	Absent P_2 (single S_2)*
	Ejection click at aortic area
	Continuous flow murmurs (collaterals)
X-ray	*Coure-en-sabot* appearance*
ECG	RVH

*characteristic clinical features

Diagnosis is based on:

- *Chest X–ray* showing *Cour en sabot appearance* or boot-shaped heart **(Fig. 17.9.1)** due to RVH with absent pulmonary conus and oligemic lung fields. Right-sided aortic arch is present in 25% cases.
- *ECG* showing *RVH with right axis deviation.*
- *Echocardiography* to—(a) establish exact location and severity of various lesions, (b) size of pulmonary vessels before surgery, (c) presence of associated abnormalities, e.g. anomalous origin of coronary vessels. *Doppler studies* help to assess the pressure gradients between various chambers, specially across the pulmonary valve.
- *Cardiac catheterization* is essential before surgery for precise assessment of structural defects and hemodynamic status. Selective right ventriculography or aortography may also be needed in some cases.

Management of ToF may be divided into—(a) medical management of cyanotic spells, (b) prevention and treatment of complications, (c) palliative measures to increase PBF, and (d) definite surgical correction.

a. ***Management of cyanotic spells*** includes:

- *Knee-chest position* to increase peripheral vascular resistance (and thus LV pressure) and decrease systemic venous return (and thus RV pressure), which helps to reduce Rt > Lt shunt.
- *Humidified oxygen support,* to improve oxygenation;
- IV fluid bolus of Normal saline 10–20 ml/kg;
- SC/IV morphine 0.1–0.2 mg/kg for sedation, to relieve anxiety and metabolic demands.
- β-blockers, e.g. IV Metoprolol (0.1 mg/kg over 5 min) to relieve infundibular spasm and reduce heart rate that improves ventricular filling. It can be repeated every 5 min if no hypotension or bradycardia, IV Esmolol infusion (50–200 mg/kg/min) may also be used in these cases.
- Correction of metabolic acidosis by IV sodium bicarbonate (1–2 mEq/kg) therapy, as required.
- Peripheral vasoconstrictors, e.g. IV/IM Methoxamine 0.1–0.2 mg/kg/dose to increase peripheral vascular resistance and LV pressure, thus to decrease Rt > Lt shunt.

- Refractory cases may need IV Phenylephrine infusion (2–5 µg/kg/min), IV Ketamine bolus (0.25–1.0 mg/kg) or rarely, general anesthesia.

b. ***Prevention of complications*** includes:

- *Cyanotic spells* by continuous propranolol therapy (PO 0.5–1.0 mg/kg/dose qds)
- *Thromboembolic complications* by avoidance of dehydration. Severe polycythemia may need repeated phlebotomy or plasmapheresis to maintain hematocrit between 45–50%.
- *Anemia* by regular iron supplementation.

c. ***Palliative measures to increase PBF*** include:

- *IV prostaglandin E_1 infusion* (0.05–0.2 mg/kg/min) may be used in newborns with severe cyanosis, as a temporary measure to keep the ductus arteriosus patent, till surgery is arranged.
- *Palliative surgery* is indicated in young and sick infants below 4 months with recurrent cyanotic spells, unlikely to withstand definitive correction. It aims to create an aortopulmonary communication (*akin* to ductus arteriosus), to augment the PBF. Most commonly used palliative surgery is *Blalock-Taussig shunt with or without Gortex conduit* between ipsilateral subclavian and pulmonary artery. Other approaches, e.g. *Potts shunt* between left pulmonary artery and descending aorta or *Waterson shunt* between right pulmonary artery and ascending aorta are rarely used. Presence of near-normal size pulmonary artery is essential for palliative surgery.

d. ***Definitive repair*** is indicated as a primary procedure in stable, minimally cyanosed cases or after palliative surgery at 6–12 months of age, using *Broke procedure*, i.e. closure of VSD and reconstruction of pulmonary valve.

Patient with absent pulmonary valve, if stable, must be managed medically till 1 year of age followed by total correction with repair of pulmonary artery branch dilation/aneurysm.

Operative mortality is ~2–5% and important postsurgical complications include arrhythmia, heart blocks and residual VSD or PS. Surgery is contraindicated in cases with hypertensive MAPCAS and severe ventricular dysfunction. Life-long infective endocarditis prophylaxis is indicated in operated cases.

2. Transposition of Great Arteries (TGA)

Transposition of great vessels/arteries (TGA) is the second commonest cyanotic CHD, characterized by *reversal of the ventricular origin of great vessels*, i.e. *aorta arising from the RV and pulmonary artery from the LV*.

Hemodynamically in TGA, systemic and pulmonary circulation run parallel to each other and survival depends on presence of some communication between two sides, e.g. ASD, VSD or PDA, to allow mixing of oxygenated and unoxygenated blood. PS may/may not be present.

Anatomically, TGA may be *complete* (as discussed above) or *corrected* in which, atrioventricular drainage is also reversed with RA draining in LV and LA in RV. Corrected TGA is usually asymptomatic unless other malformations are present, as the serial circulation between systemic and pulmonary flow is re-established.

Clinical features of complete TGA depend on the presence or absence of VSD and PS.

- TGA *without* VSD/PDA manifest soon after birth with cyanosis and CCF.
- TGA *with* VSD/PDA but *without* significant PS usually present by 6–10 weeks with CCF.
- TGA *with* VSD/PDA *as well as* significant PS present usually by 6–10 weeks with cyanosis.

Auscultatory findings vary according to the type of lesion and have limited diagnostic value.

Diagnosis is supported by:

- *Chest X-ray* showing *egg on string appearance*, i.e. RVH with narrow base due to anteroposterior location of great vessels. Lung fields may be plethoric, normal or oligemic, depending on the severity of PS.
- *ECG* showing RVH with right-axis deviation, though biventricular hypertrophy or LVH may be present in cases with large VSD.
- *Echocardiography* is diagnostic, though cardiac catheterization is essential before surgery for precise assessment of the severity of lesions.

Management: Complete TGA needs early surgical intervention after stabilization of the patient and control of CCF. *Prostaglandin E_1 infusion* is advised in severely cyanosed newborns to keep the ductus patent, till surgery is arranged.

Simple TGA or TGA with CoA should operated at 2–4 weeks or earlier if symptomatic. TGA with large VSDs must be operated by 6–8 weeks due to risk of early pulmonary vascular disease.

- *Palliative* ***Rashkind balloon atrial septostomy*** is indicated in very young and sick infants, to create an additional site (ASD) for mixing of systemic and pulmonary flow.
- *Definite repair* in younger infants involves **Jatene arterial switch operation**, i.e. resection of aortic and pulmonary trunk and re-anastamosis of distal aorta with proximal pulmonary trunk and *vice versa*, along with closure of VSD and bending of pulmonary artery. Other atrial-switch procedures, e.g. *mustard* or *senning* operation may be used in older children with small regressed LV but carry significant long-term morbidity.

3. Total Anomalous Pulmonary Venous Drainage (TAPVC)

Total/partial anomalous pulmonary venous drainage (TAPVD/PAPVD) is an uncommon cyanotic CHD, characterized by *anomalous drainage of all or some pulmonary veins into RA, superior vena cava or even portal vein, instead of LA*.

Hemodynamically in these cases, mixing of oxygenated and unoxygenated blood occurs in RA, while LA receives blood only *or* partially through fossa ovalis/ASD. Increased blood flow in RA and then to RV, leads to RVH. PS is commonly present.

Clinical presentation depends on the extent of anomalous drainage and presence/severity of PS. Cases with significant PS usually manifest with cyanosis in second week of life, while those without PS manifest with CCF after neonatal period. Auscultatory findings are similar to ASD, i.e. *wide and fixed split of S_2 and ESM* at pulmonary area, along with a *venous hum* in suprasternal or left infraclavicular region due to abnormal pulmonary veins.

Diagnosis rests on:

- *X-ray chest* showing '*Snowman in storm*' or *'Figure of 8 appearance'*, due to abnormal position and dilatation of pulmonary veins with RVH.
- *ECG* shows RVH and right-axis deviation, usually associated with *'P' pulmonale* suggestive of RA dilatation and *rsR' pattern* suggestive of RV strain in right chest leads.
- *Echocardiography* is diagnostic, though cardiac catheterization is essential before surgery for precisely assessment of the severity of lesions.

Management: Apart from supportive medical therapy (as for other cyanotic CHDs), treatment is essentially surgical. Surgery is indicated as early as possible in cases with TAPVD, as unoperated cases are unlikely to survive beyond 3 months. However, cases with PAPVD may survive for many years.

4. Tricuspid Atresia (TA)

Tricuspid atresia (TA) is a rare cyanotic CHD, characterized by *congenital absence of tricuspid valve.*

Hemodynamically, RA outflow obstruction leads to gross RA dilatation with Rt > Lt shunt via fossa ovalis or ASD, which is essential for survival. Additional flow in LA and LV leads to LVH. RV is hypoplastic and pulmonary circulation is sustained by a Lt > Rt shunt via VSD/PDA. PS is common.

Clinical presentation depends on the adequacy of Lt>Rt shunt at ventricular/ductal level. Most cases present at birth with cyanosis, LVH, pansystolic murmur of VSD, single S_2 due to PS and pathognomonic *prominent 'a' waves in jugular veins* (due to RA contraction against atretic tricuspid valve).

Diagnosis is supported by—(a) *X-ray chest* suggestive of marked RA dilatation, LVH and oligemic lung fields, and (b) *ECG* showing LVH, left-axis deviation and *'P' pulmonale*. It needs to be confirmed on echocardiography and/or cardiac catheterization.

Treatment includes a palliative *Blalock-Taussig shunt* in neonatal period, followed by *modified Fontan operation* at a later date, i.e. anastomosis of IVC and PA to bypass right heart. Prostaglandin E_1 infusion is advised in severely cyanosed newborns to keep the ductus patent, till surgery is arranged.

5. Ebstein Anomaly (EA)

Ebstein anomaly is characterized by *downward displacement of abnormal tricuspid valve into the right ventricle,* i.e. *atrialization of right ventricular cavity above the valve* and consequent obstruction in RA outflow.

Hemodynamically, obstruction of the RA outflow tract leads to dilatation of RA and Rt > Lt shunt via fossa ovalis or ASD. Like tricuspid atresia, pulmonary flow in Ebstein anomaly is also largely dependent on VSD or PDA.

Clinically, these cases present at any age with exertional dyspnea, cyanosis or recurrent paroxysmal tachycardia. Important auscultatory findings include a *typical scratchy murmur* resembling pericardial rub in left parasternal area due to turbulence at tricuspid valve, with/without a PSM of associated VSD.

Diagnosis is supported by—(a) chest skiagram showing *marked RA dilatation and LVH, and (b)* ECG showing LVH, *'P' pulmonale* due to RA abnormality and *'P' mitrale* due to LA volume overload. It needs to be confirmed on echocardiography. Cardiac catheterization is necessary before surgery.

Management depends on the severity of defect. *Surgical therapy* aims to provide palliative treatment in newborns with severe cyanosis, i.e. closure of tricuspid valve by a synthetic patch, atrial septostomy and aortopulmonary shunt *(Stranes procedure)*, followed by definitive *valvuloplasty* at a later date. Milder cases may be left untreated or taken directly for valvuloplasty in late childhood.

17.5.4 DIAGNOSTIC APPROACH IN CHD

Presence of a murmur, by itself, does not necessarily indicate heart disease in children, as ~15–20% infants have functional murmurs due to relatively high blood volume, hyperdynamic blood flow and smaller size of valves.

Diagnostic approach towards a child or infant with murmur revolves around following questions:

a. Whether a heart disease is present?
b. If yes, whether it is congenital or rheumatic?
c. If congenital, whether it is acyanotic or cyanotic?

TABLE 17.21: Nadas' criteria

Major (any one)	*Minor (any two)*
Systolic murmur >Gr III*	Systolic murmur <Gr III
Diastolic murmur (any)	Abnormal S_2
Cyanosis	Abnormal X-ray chest
CCF	Abnormal ECG Abnormal BP

*i.e. with thrill

TABLE 17.22: D/D between CHD vs. RHD

	CHD	*RHD*
Age of onset	< 5 years*	> 5 years
History	Family history of CHD	Past history of RF
Type of lesion	Shunt lesions Valvular (AR, AS, PS)	Valvular (MR, MS, AR)
Assoc. features	Cyanosis Congenital malformations Intrauterine infection	Arthritis, S/C nodules

d. Whether it is associated with increased PBF or decreased/normal PBF?
e. Whether it is associated with RVH or LVH?
f. Whether any complications, e.g. CCF, infective endocarditis or arrhythmia are present?

TABLE 17.23: D/D between LVH and RVH

	LVH	*RVH*
Clinical:		
Apex beat	Lateral, downward	Lateral
Parasternal heave	Absent	Present
Epigastric pulsations	Absent	+/–
***Chest X-ray* (Apex)**	Lateral, downward	Lateral
ECG	Deep S (V_{1-2}), Tall R (V_{5-6}) Left axis	Tall R (V_{1-2}), Deep S (V_{5-6}) Right axis

Step I. Whether a heart disease is present?

Nadas criteria **(Table 17.21)** is very useful to answer this question in young children. *Presence of any one major or two minor criteria strongly indicate presence of organic heart disease*. Functional murmurs are common in infancy as well as in older children with hyperdynamic flow, i.e. severe anemia, thyrotoxicosis, beriberi, and large A-V fistula.

Step II. Whether it is congenital or rheumatic HD?

Important differences between CHD and RHD are shown in **Table 17.22**, most important being the age of presentation. While ~75% of CHDs manifest by the end of infancy, RHDs are extremely rare before 5 years. However, ASDs, small VSDs and mild congenital valvular lesions, e.g. MR, PS, AS or mitral valve prolapse may be easily missed in early life.

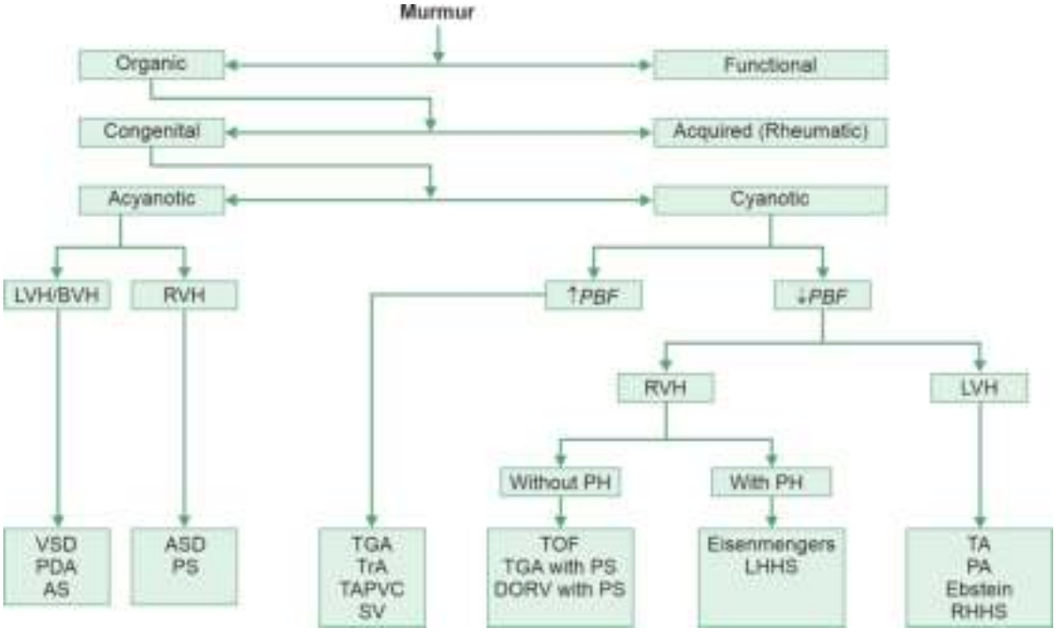


Fig. 17.19: Diagnostic algorithm for CHDs.

LVH/RVH/BVH: Left/Right/Bi-ventricular hypertrophy; **PBF:** Pulmonary blood flow; **VSD:** Ventricular septal defect; **PDA:** Patent ductus arteriosus; **ASD:** Atrial septal defect; **PS:** Pulmonary stenosis; **TGA:** Transposition of great arteries; **TrA:** Truncus arteriosus; **TAPVC:** Total anomalous pulmonary venous drainage; **SV:** Single ventricle; **DORV:** Double outlet right ventricle; **LHHS:** Left hypoplastic heart syndrome; **TA:** Tricuspid atresia; **PA:** Pulmonary atresia; **RHH:** Right hypoplastic heart syndrome.

Step III. Whether it is acyanotic or cyanotic?

Presence of cyanosis differentiates Rt > Lt shunts from Lt > Rt shunts or simple obstructive lesions. However, it is important to note that:

- Cyanosis is often absent at birth in Rt > Lt shunts due to high pulmonary arterial pressure in relatively unexpanded lungs and appear after variable duration, depending on the severity of shunt and pressure gradients. Thus, absence of cyanosis at birth does not exclude cyanotic CHDs.
- Mild duskiness may develop in severe Lt > Rt shunts or obstructive lesions during excessive crying or heavy exercise due to compromised pulmonary blood flow. However, unlike cyanotic CHDs, it is easily relieved on rest or oxygen therapy *(Hyperoxia test, see* Chapter 17.2*).*
- Presence of clubbing, cyanotic spells, squatting posture and failure to thrive (without CCF) strongly indicates cyanotic CHD.

Step IV. Whether pulmonary blood flow is increased, decreased or normal?

- Increased pulmonary blood flow is indicated by—(a) recurrent chest infections, (b) breastfeeding difficulties (suck-rest-suck cycle), (c) plethoric lung fields on chest X-ray, and (d) Loud P_2.
- Absence of these features or absent P_2 indicates normal/decreased pulmonary blood flow.

Presence of cyanosis or dyspnea alone, is not a reliable indicators of pulmonary blood flow.

Step V. Whether it is with RVH or LVH?

Important diagnostic differences between RVH and LVH are shown in **Table 17.23**.

Step VI. Whether complications, e.g. CCF, infective endocarditis or arrhythmia are present?

Clinical features of these complicating events have been discussed in respective chapters.

A diagnostic algorithm for common CHDs, based on above observations is presented in **Fig. 17.19**.

17.6 RHEUMATIC FEVER

Rheumatic fever (RF), the leading cause of heart disease in school-age children, is an acute inflammatory disease affecting the joints, heart, skin, subcutaneous tissue and nervous system, following streptococcal sore throat (SST).

Incidence: RF is widely prevalent in overpopulated developing countries like India, though the incidence has declined in recent years to ~1–3% of school children. However some western countries have witnessed resurgence of RF during last two decades. Recent data suggests ~0.5–1.0% of Indian school children have evidence of rheumatic heart disease.

Epidemiology of RF closely follows the epidemiology of SST, both being common in—(a) school-children aged 5–14 years, (b) low socioeconomic status, (c) overcrowded slum population, and (d) rainy, winter or early spring season. Both sexes are equally affected, though chorea and mitral valve disease is more common in females, while aortic valve disease is common in males.

Etiopathogenesis: RF follows an attack of pharyngeal infection by ~2–3 weeks, due to rheumatogenic strains of *Group A β-hemolytic streptococci* (M type 1, 3, 5, 6, 18 and 24).

While the association between RF and streptococcal sore throat (SST) is well known, exact pathogenesis of RF is not clearly established, seems to be an *abnormal immune-mediated damage* to various tissues, due to:

- *Cross-reactivity* of anti-streptococcal antibodies with some human tissues antigens in susceptible organs, e.g. heart, bones and CNS, which are structurally similar to streptococcal antigens;
- *Autoimmunity* due to modification of human tissues by direct streptococcal infection, which are then themselves recognized as foreign and initiate autoantibody production.

As only 1–3% of SST develop RF, an underlying genetic susceptibility has also been postulated.

Pathology: RF is characterized by involvement of various organs and tissues including the heart, joints, skin and nervous system.

Cardiac pathology affect all the layers of the heart (pancarditis) including:

- Valvulitis, with formation of vegetations on *valvular edges*, which heals with fibrosis to cause residual deformity and RHD.
- Myocarditis, characterized by perivascular aggregation of pathognomonic *Aschoff bodies*-large multi-nucleated giant cells around a vascular core of fibrinoid material.
- Serofibrinous pericarditis, pathologically resembling *bread and butter appearance*.

Joint pathology presents with inflammatory swelling of articular and periarticular structures with minimum exudation, but no erosion, pannus formation or residual lesion (d/d rheumatoid arthritis).

Subcutaneous nodules are localized granulomas (resembling Aschoff bodies) with fibrinoid swelling of collagen bundles and perivascular collections of histiocytes, fibroblasts and lymphocytes.

Neuropathology is non-specific (cellular degeneration and hyalinization of small blood vessels), non-localized and does not correlate with clinical findings. *Aschoff bodies are never seen in brain.*

Clinical manifestations of RF begin after a latent period of 2–3 weeks of SST, with or without nonspecific complaints, e.g. low/moderate fever and constitutional symptoms.

Characteristic manifestations of RF include *arthritis, carditis, chorea, subcutaneous nodules and erythema marginatum*, though not more than one or two of them develop during the same episode. Natural history is highly variable with different manifestations on different time-frames—arthritis and carditis as early manifestations (2–3 weeks), subcutaneous nodules as an intermediate manifestation (3–6 weeks), and chorea as late manifestation (>3 months).

Rheumatic arthritis, is the commonest manifestation of RF (75%), characterized by:

- *Polyarticular* involvement of large joints, e.g. knee, ankle, elbow and wrist, sparing digital joints and spine.
- *Migratory* character, involving only 1–2 joints at one time, which spontaneously recover within 48–72 hours, only to recur in other joints. Total course of arthritis does not exceed 2–4 weeks, even in untreated cases.
- *Disproportionately more pain* than other signs of inflammation, e.g. swelling. Some cases have only arthralgia. Joint X-rays.
- *Complete recovery*, without residual deformity. Chronic *Jaccoud's arthropathy* is an extremely rare complication after multiple, prolonged attacks.

Rheumatic carditis, seen in 40–50% cases of first attack and 70–80% cases of subsequent attack, is the most dreaded manifestation of RF due to acute morbidity as well as risk of residual heart disease.

Usually seen after 2–3 weeks of arthritis, rheumatic carditis may be asymptomatic or present with palpitation, exertional dyspnoea and various signs of pancarditis **(Table 17.24)**. One or more valves may be involved, commonest being mitral valve (95%), followed by tricuspid (10–30%) and aortic valve (5%). *Pulmonary valve is almost always spared.* Active carditis may continue for 3–4 months, irrespective of treatment. Residual lesions develop in ~50–75% cases of first attack and in almost all cases on subsequent attacks.

Rheumatic (Sydenham) chorea, seen in ~10–15% cases, is a late manifestation of RF which presents after many months with insidious onset of:

- *Emotional instability*, e.g. inappropriate smiling, crying or restlessness (earliest indicator).
- *Clumsy movements* with deterioration of handwriting.
- *Typical choreiform movements* — rapid, jerky, quasi-purposeful movements at proximal joints, e.g. shoulder, which disappear in sleep and aggravate during activity.
- Generalized hypotonia/dystonia.
- Occult signs, e.g. *milk-maid grip* (intermittent contraction and relaxation of hand-grip, while holding the examiner's finger) and *Lizard-tongue* or *tongue in jack-box* appearance (fasciculations and ill-sustained protrusion of tongue)

Evidences of preceding SST, e.g. ASO titers or acute phase reactants, e.g. ESR, are absent in rheumatic chorea.

Subcutaneous nodules, seen in only 5% cases, are firm, non-tender nodules of 1–2 cm, covered with normal skin. Mainly seen over occiput, spine, shin of tibia and extensor aspects of joints, these nodules last only for a few days. *Presence of subcutaneous nodules almost always indicates presence of carditis.*

Erythema marginatum is an evanescent, non-pruritic, pinkish-red macular rash with serpiginous margins, not well visible in dark-skinned Indian children.

Other manifestations, e.g. abdominal pain, epistaxis and pneumonia are not uncommon in RF but have no diagnostic or prognostic value.

Diagnosis of RF depends on ***Revised Jones criteria 2015*** **(Table 17.25)** which differs in low-risk populations and moderate/high-risk population, classified according to incidence of RF in school children (</>2/100,000) or prevalence of RHD in general population (</>1/1000).

Presence of two major criteria or one major and two minor criteria in presence of essential criteria, i.e. any evidence of previous streptococcal infection, e.g. positive throat culture, history of scarlet fever or raised antistreptolycin (ASO) titers, suggests diagnosis of RF. Even the presence of three minor criteria (without major criteria) is considered as suggestive of RF in a case with past history of RF.

TABLE 17.24: Clinical signs of rheumatic carditis

- Tachycardia — disproportionate to fever
- Muffling of heart sounds
- Abnormal gallop/tic-tac rhythm
- Changing murmurs or Carey Coombs' murmur
- Cardiomegaly
- Congestive cardiac failure
- Pericardial rub

TABLE 17.25: Revised Jones criteria (2015) for acute RF

Low-risk population	*High-risk population*
Major criteria	
Carditis * Polyarthritis Chorea Erythema marginatum Subcutaneous nodules	Carditis* Polyarthritis or monoarthritis Polyarthralgia Chorea Erythema marginatum Subcutaneous nodules
Minor criteria	
Polyarthralgia Fever > 38.5°C ESR >60 mm/CRP >3 mg/dl Prolonged PR interval**	Monoarthralgia Fever >38°C ESR >30 mm/CRP >3 mg/dl Prolonged PR interval
+ Essential criteria: Previous evidence of streptococcal infection***	

*including subclinical carditis on echocardiography
**for age
***Positive throat culture *or* history of scarlet fever *or* elevated ASO titers

Laboratory investigations: No single test is diagnostic of RF, though supporting investigations include:

- ***Evidence of streptococcal infection (Essential criteria)*** like:
  - *Elevated ASO titers* (>333 Todd units *or* >200 Todd units and rising). Elevated anti-DNAase-B or anti-hyaluronidase titers are more specific, while anti-streptozyme test is more sensitive that also detects extra-cellular streptococcal antigens.
  - *Positive throat culture* is not necessarily diagnostic, as carriers are common. Similarly, negative culture does not exclude RF.
- ***Evidence of inflammatory process*** (*acute phase reactants)*, e.g. elevated ESR >30 mmFHR (>60 mm in low-risk population) or CRP > 3 mg/dl is considered as a minor criteria for diagnosis of RF. ESR also has important prognostic value in assessing the course and therapeutic response.
- ***Evidence of cardiac involvement*** on:
  - *ECG: Prolonged PR interval for the age* is common in RF, even without clinical carditis.
  - *Echocardiography* may reveal cardiac dilatation, valvular abnormalities, pericardial effusion and LV dysfunction. Vegetations are rarely seen. Echocardiographic evidence of carditis is enough as a major criteria, even in absence of clinical carditis.

Management of RF needs hospitalization for monitoring the progression of disease, though chorea, if not debilitating, may be managed at home. Important steps in management include:

a. **Eradication of streptococcal infection** with penicillin, either as single IM benzathine penicillin (12,00,000 U >9 years/6,00,000 U <9 years) or daily IM procaine penicillin (50,000 U/kg/OD) for 10 days. In penicillin-allergy, Erythromycin (40–50 mg/kg/d q8hrx 10 days) or Azithromycin (10 mg/kgOD x 5days) may be used.

b. **Anti-inflammatory therapy** with salicylates or steroids, is the cornerstone of management in rheumatic arthritis or carditis, as follows:
   - *Rheumatic arthritis* or *rheumatic carditis without CCF or cardiomegaly* is treated with PO Aspirin 50–70 mg/kg/day q6hr for 3–5 days, then 50 mg/kg/day q6hr for 3 weeks, and then 25 mg/kg/day for next 4–6 weeks.
   - *Rheumatic carditis with CCF or cardiomegaly* is treated with PO Prednisolone 2 mg/kg/day q6hr for 2–3 weeks, followed by 1 mg/kg/day q6hr for 2–3 weeks and then tapered by 5 mg/kg/day every 2–3 days. While initiating the tapering doses of steroids, Aspirin PO 50 mg/kg/day q6hr must be added for 6 weeks.
   - *Rheumatic Chorea* or other manifestations do not need anti-inflammatory therapy, but presence of carditis must be excluded.

c. **Supportive treatment** includes bed rest, and treatment of CCF or other symptoms.
   - Strict bed rest is indicated only in cases with impending or established CCF, though restriction of strenuous activity is desirable in presence of carditis or arthritis.
   - *Arthralgia,* without arthritis must be treated only with paracetamol or codeine, so as not to mask the progression.
   - *Chorea* may be treated with usual doses of non-specific sedatives, e.g. phenobarbitone, haloperidol, diazepam and chlorpromazine, etc., for symptomatic relief.
   - No treatment is required for subcutaneous nodules or erythema marginatum.

d. **Monitoring:** Cases with arthritis or carditis should be closely monitored for appearance of carditis or CCF respectively, and to assess the response to anti-inflammatory therapy. *ESR is a reliable indicator for laboratory monitoring of rheumatic activity*.

Prevention of RF includes:

Step I. Primary prevention, before the first attack of RF involves:

- Prevention of SST in general population by community measures, e.g. avoidance of overcrowding.
- Early diagnosis and treatment of SST with single dose of IM Benzathine Penicillin 12 Lac U (6 Lac U in children <27 kg) or PO Penicillin V 250 mg QID for 10 days. Alternatively, PO Cephalexin 15–20 mg/kg BD for 10 days or PO Azithromycin 12.5 mg/kg OD for 5 days may also be used.

Step II. Secondary prevention to prevent recurrence of RF after the first attack. Since children with past history of RF are at higher risk of recurrence after subsequent SST (>30% vs 1–3% in general population), all of them should receive secondary prophylaxis with IM Benzathine penicillin G (12 Lac U *every 21–28 days* (6 Lac U every 15 days in children <27 kg). Alternatives include-PO Penicillin V (250 mg BD daily) in cases who refuse to take IM injections, *or* PO Erythromycin (20 mg/kg BD daily) in penicillin allergy.

While recommendations for the duration of secondary prophylaxis vary, IAP recommends that it should continue for at least:

- *5 years after the last attack or till 21 years of age, whichever is later, in cases of RF without carditis,*
- *10 years after the last attack or till 21 years of age, whichever is later, in carditis without residual heart disease.*
- *10 years after the last attack or till 40 years of age, whichever is later, in cases with residual heart disease*

17.7 RHEUMATIC HEART DISEASE

Rheumatic heart disease (RHD) is the commonest sequel of RF, due to residual thickening, scarring and deformity of valvular anatomy after acute valvulitis in RF. Recurrent attacks increase the risk and severity of valvular damage. Recent data suggests ~ 0.5–1.0% of Indian school children have evidence of rheumatic heart disease.

Common organic valvular lesions in RHD are left-sided, i.e. MR, MS and AR in order of frequency, either alone or in combinations. Rheumatic AS is extremely rare before 20 years of age. Right-sided lesions are usually functional and regurgitant, due to back-pressure from left-sided lesions, though TR may be organic. Pulmonary valve is almost always spared in RF.

Mitral Regurgitation (MR)

Mitral regurgitation is the commonest valvular lesion in acute carditis as well as in established RHD (>90%), characterized by *reverse leak from LV to LA during ventricular systole* due to deformed and incompetently closed MV. Severity of MR is maximum during acute carditis and tends to diminish gradually, may even disappear in >50% cases by 1 year of acute attack.

Hemodynamics and consequent genesis of clinical signs in MR includes:

- Incompetent closure of MV leading to *muffed S1*.
- Regurgitation of LV blood in LA during ventricular systole due to defective MV closure, producing *high pitched apical pansystolic murmur that radiates towards the axilla, with/without thrill*.
- Dilatation of LA to accommodate regurgitant flow. However, as there is no obstruction to LA outflow, mean LA pressure does not rise significantly. Consequently, *pulmonary venous hypertension and CCF due to back-pressure is uncommon (unlike MS) except in cases with associated severe MR or acute carditis*, when LA could not dilate enough due to rapidity of lesion.
- Volume-overload over LV, as it: (a) receives more blood from LA during next cycle, and (b) has to contract more forcefully to maintain cardiac output, leading to *LVH*, i.e. *downward and outward shifting of apex beat with heaving character*.
- Increased LA > LV flow through MV in diastole due to additional LA volume, may produce *III heart sound* and/or a short *diastolic flow murmur* (functional) at apex in severe MR. Hence, *presence of an apical mid-diastolic murmur in MR does not necessarily mean co-existing MS*.
- LV pressure drops rapidly during systole due to MV leak, leading to *mild water-hammer pulse* and *split* S_2 by early closure of AV in severe cases. Hence, *widely split* S_2 *in MR does not necessarily mean PH*.

Clinical presentation: Unlike MS, MR is an early lesion in RHD, often in continuation of acute carditis (no latent period). While mild cases may be asymptomatic, moderate/severe cases present with signs of reduced cardiac output (exertional dyspnoea, easy fatigability) or compensatory cardiac overactivity, e.g. tachycardia/atrial arrhythmia (palpitation).

CCF and PH is rare in MR and indicates possibility of *acute carditis, severe lesion* or *co-existing MS*.

Important cardiac signs include—(a) LV heaving apex beat, shifted downward and laterally, (b) muffled FHS, (c) apical PSM radiating to axilla, with/without (d) apical flow MDM, and (e) audible S3 **(Fig. 17.20)**.

Complications include: (a) CCF/PH in severe disease, (b) atrial arrhythmias, (c) infective endocarditis, and (d) development of supervening MS.

Diagnosis is supported by:

- X-ray chest suggestive of LVH,
- ECG suggestive of LVH and

Echocardiography suggestive of—(a) increased LV and LA dimensions, (b) hyperdynamic motion of septum, (c) thickening/calcification of anterior MV leaflet, and (d) regurgitant flow on pulse/color Doppler studies.

D/D includes other cause of MR **(Table 17.26)**, commonest being mitral valve prolapse, discussed later.

Treatment depends on the severity of disease and include—(a) rheumatic and infective endocarditis prophylaxis, (b) treatment of complications, e.g. CCF, infective endocarditis or arrhythmia, and (c) *afterload reducing agents*, e.g. captopril, in selected cases to improve cardiac output and consequently, to reduce the regurgitant flow through MV.

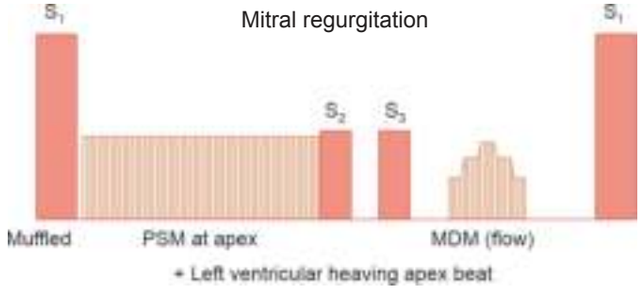


Fig. 17.20: Important cardiac signs in MR.
PSM: Pansystolic murmur; **MDM:** Mid-diastolic murmur

TABLE 17.26: Causes of MR

- **Rheumatic MR**
- **Congenital**
  - Mitral valve prolapse (MVP)
  - MR with/without osteum primum ASD.
  - *Collagen defects:* Marfan syndrome, Hurler syndrome
- **Acquired** (due to LV dilatation)
  - Cardiomyopathies, myocarditis, etc.
  - Infective endocarditis, papillary muscle dysfunction
  - Functional MR in AR (due to LV dilatation)

Surgical correction with *valve repair (annuloplasty) or valve replacement* is indicated in cases with—(a) refractory CCF, (b) progressive LV dilatation on ECHO, (c) severe pulmonary hypertension and (d) complications, e.g. ruptured chordae or recurrent infective endocarditis. Annuloplasty is preferred in children to avoid long-term anticoagulant therapy, essential after replacement surgery.

Mitral valve prolapse (MVP) is a common congenital abnormality, echocardiographically detectable in ~15–20% of population. It is characterized by billowing of one or both cusps into LA during ventricular systole.

MVP is more common in females and those with similar family history, Marfan syndrome, pectus excavatum, etc.

Clinically, most cases are asymptomatic and diagnosed accidentally due to presence of a typical *musical late systolic murmur, sometimes preceded by a click*.

MVP is non-progressive and no treatment is necessary in childhood after initial evaluation. Rarely, complications, e.g. arrhythmias, strokes, infective endocarditis and CCF may develop in later life.

Mitral Stenosis (MS)

MS is a late lesion in RHD due to fibrosis of valvular ring, commissural adhesions and thickening or calcification of valvular leaflets, restricting their mobility. Although develops much earlier in Indian than in western children, it takes at least ~2 years to develop established MS after an acute attack of RF. MS accounts for ~10% of all pediatric RHDs, either alone or in combination with MR or other valvular lesions.

Hemodynamics and consequent genesis of clinical signs in MS includes:

- Turbulence in LA>LV flow due to narrowed MV (Normal size: ~5 cm^2), producing *localized mid-diastolic murmur with presystolic accentuation* at apex, best heard in expiration and left lateral position with bell of the stethoscope. MDM may disappear during CCF.
- Delayed but forceful closure of MV, leading to pathognomonic *loud* S_1. Absence of loud S_1 indicates very tight or calcified MS.
- LA dilatation (volume-overload) due to obstructed outflow with consequent increase in LA pressure. LA volume-overload necessitates early and forceful opening of MV during diastole, presenting as *opening snap (OS)* just after S_2, which may be absent in tight or calcified MS.
- Rise in pulmonary venous pressure due to back pressure from LA, leading to pulmonary venous hypertension (PVH) and consequent pulmonary congestion/edema, which presents as progressive dyspnea, cough, frothy or rusty sputum and basal crepitations in lungs.
- Rise in pulmonary arterial pressure, first slowly and passively due to PVH and then rapidly and actively by pulmonary arteriolar constriction to maintain adequate PA-PV pressure gradient, leading to pulmonary arterial hypertension (PAH). PAH presents with—(a) loud P_2 that may also be palpable (diastolic shock), (ii) wide-split S_2 due to delayed PV closure, and (iii) early diastolic murmur at lower sternal border (*Graham-Steel murmur*) due to functional PR.
- Rise in RV pressure due to PAH with consequent RVH, presenting as *left parasternal heave*, tricuspid pansystolic murmur (functional TR) and CCF. RVH also lead to typical *tapping apex beat* in MS, as the posterior RV pushes the LV forward.

Clinical presentation depends on the severity of MS and includes signs of:

- *Chronic pulmonary congestion*, e.g. progressive dyspnea, orthopnea, paroxysmal nocturnal dyspnea and recurrent chest infections, orthopnea and nocturnal dyspnea are early features in MS, due to pooling of blood in the lungs in lying-down position.
- *Acute pulmonary edema*, e.g. cough, frothy and rusty (blood-tinged) sputum and respiratory distress.
- *CCF*, e.g. pedal edema, hepatomegaly, raised JVP, etc.
- *Systemic venous stasis*, e.g. malar flush *(Mitral facies)*
- *Reduced cardiac output*, e.g. easy fatigability, syncopal attacks, etc.

Important clinical signs in MS include-(a) loud first HS, opening snap, (b) mid-diastolic murmur with late accentuation and (c) loud second HS after development of pulmonary hypertension **(Fig. 17.21)**.

Severity of MS may be judged by-(a) absence of S_1 or opening snap due to calcified valve, (b) lesser time distance between opening snap and aortic component of S_2, and (c) severe PAH.

Complications of MS include—(a) pulmonary edema, (b) CCF, (c) infective endocarditis, (d) arrhythmia, and (e) thromboembolic complications due to LA hemostasis and thrombus formation.

Diagnosis is supported by:

- *X-ray chest* suggestive of—(a) RVH, i.e. outward shifting of apex beat, (b) straightening of left cardiac

Fig. 17.21: Important cardiac signs in MS.
OS: Opening snap; **MDM:** Mid-diastric murmur

border due to enlarged LA appendages (*mitralization*), and (c) pulmonary venous congestion (*Kerley B lines*) or pulmonary edema *(diffuse haziness*).

- *ECG* suggestive of—(a) RVH with Rt axis deviation, and (b) *P mitrale*-wide-notched P wave of LA dilatation.
- *Echocardiography* suggestive of—(a) decreased MV leaflet movements (E-F and D-E slope) on M-mode, (b) LA dilatation with decreased MV size on 2-D echo, and (c) increased transmitral pressure gradient on Doppler studies. Echocardiography also help to assess severity of PAH and exclude complications, e.g. infective endocarditis and LA thrombus.

D/D includes o*ther rare causes of MS*, e.g. congenital MS, endomyocardial fibroelastosis and Lutembacher syndrome (acquired MS with ASD) *or conditions mimicking MS hemodynamics*, e.g. LA myxoma, ball-valve LA thrombus or Cor triatriatum.

Treatment includes—(a) restricted physical activity, (b) rheumatic and infective endocarditis prophylaxis, (c) treatment of complications, e.g. CCF, infective endocarditis or arrhythmia, and (d) surgery.

Surgical intervention in MS depends on the type of lesion, as follows:

- *Transcutaneous balloon valvuloplasty* is the treatment of choice for non-calcified valves, as early as possible before significant PAH develops. Due to lesser risk, cost and duration of hospitalization, it has nearly replaced the need for closed mitral commissurotomy, practiced earlier.
- *Open valvotomy* or valve replacement is indicated in children with—(a) calcified MV, (b) critical MS with MV size <1 cm^2, (c) co-existing MR, and (d) complications, e.g. LA thrombus.

Aortic Regurgitation (AR)

AR is rarely an isolated rheumatic lesion, usually seen along with MV disease in ~5–8% RHDs. It is characterized by *reverse leak from aorta to LV* during ventricular diastole through incompetent AV.

Hemodynamics and consequent genesis of clinical signs in AR include:

- Backward leak from aorta to LV during ventricular diastole, leading to *high-pitched blowing early diastolic (decrescendo) murmur.*
- LV volume-overload due to reverse aortic-flow, leading to LVH with *outward and downward shift of apex beat* that is *hyperdynamic (ill-sustained heave)* in character. Anginal chest pains are common in severe AR due to relative ischemia of hypertrophic myocardium.
- Dilated AV ring and regurgitant aortic flow may prevent MV to open fully, leading to a functional apical diastolic murmur (*Austin-flint murmur*).

TABLE 17.27: Peripheral signs in AR

- Wide pulse pressure >40 mm Hg
- Collapsing (*water-hammer*) pulse
- *Corrigan's sign* (dancing carotids)
- *de Musset's sign* (head-nodding during systole)
- *Quincke's sign* (↑capillary pulsations on nail bed)
- *Traube sign* (pistol-shot sound over femoral artery)
- *Duroziez murmur* (murmurs over femoral artery)*
- *Hill's sign* (lower limb BP >20 mm higher than in UL)

*Diastolic murmur on pressing the femoral artery distal to stethoscope and systolic murmur on pressing proximally.

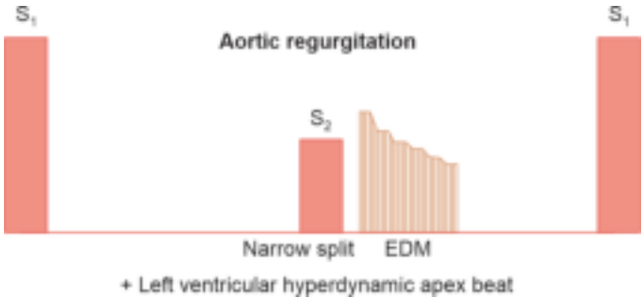


Fig. 17.22: Important cardiac signs in AR.
EDM: Early diastolic murmur (Decresendo)

- Increased LV outflow due to volume overload, may lead to—(a) *functional ejection systolic murmur at aortic area,* and (b) delayed AV closure with *narrow split of* S_2.
- A combination of increased LV outflow, followed by immediate reverse leakage from aorta (aortic run-off) is responsible for sudden drop in aortic pressure during ventricular diastole, leading to wide pulse pressure and other peripheral signs **(Table 17.27)**.
- Absence *of wide pulse pressure or water-hammer pulse in AR indicates co-existing MS or AS.*
- Pulmonary hypertension is uncommon except in severe AR, caused by back-pressure (LV > LA > PVH > PAH).

Clinically, mild cases may be asymptomatic, though severe cases present with palpitations (due to forceful LV contractions) and progressive exertional dyspnea. Anginal chest pain may be precipitated by exercise. Excessive sweating and heat intolerance is common due to peripheral vasodilatation.

On examination, collapsing pulse with wide pulse pressure along with other peripheral signs of aortic runoff **(Table 17.27)** are useful indicator of AR.

Important cardiac signs include—(a) LV heaving apex impulse, and (b) high pitched *decrescendo* ejection diastolic murmur over pulmonary area that radiates towards apex and aortic area and best audible in full expiration with patient leaning forward, (c) a functional diastolic murmur at apex (*Austin Flint murmur*) and/or ejection systolic murmur at aortic area may be present **(Fig. 17.22)**.

Diagnosis is confirmed by:

- *X-ray chest* suggestive of LVH and prominent aortic knuckle due to higher LV outflow > aortic dilatation.
- *ECG* suggestive of LVH.
- *Echocardiography* suggestive of—(a) dilated LV on M-mode, (b) diastolic flutter of anterior *MV cusp* due to regurgitant aortic flow on 2-D echo, (c) abnormal LV-aorta pressure gradient with aortic run-off on Doppler studies.

D/D of AR includes:

- *Other causes of wide-pulse pressure*, e.g. PDA, large AV fistulae, ruptured sinus of valsalva, severe anemia, thyrotoxicosis, etc.
- *Other causes of AR*, e.g. congenital AR, bicuspid AV, Marfan syndrome, aortic aneurysms, etc.

Management: Mild/moderate lesions are well tolerated though unlike MR, AR does not regress with time. Treatment includes: (a) rheumatic and infective endocarditis prophylaxis, (b) treatment of complications, e.g. CCF, infective endocarditis and arrhythmia and (c) surgery.

***Surgery** with valve replacement* is indicated in – (a) progressive LV enlargement or deteriorating LV ejection fraction (<40%), (b) development of CCF and angina.

Tricuspid Regurgitation (TR)

Although TR is present in 20–30% cases of RHD with CCF, it is rarely organic, usually caused by RV dilatation in severe left-sided lesions. Hence, the signs of TR are generally evident only during CCF due to primary RHD and disappear once it is controlled.

Important clinical signs of TR include – (a) prominent jugular venous pulsations, (b) pulsatile liver, (c) blowing pansystolic murmur over tricuspid area, best audible in inspiration; along with features of primary RHD. Valvuloplasty is rarely needed in these cases.

Diagnostic Approach to RHD

Diagnostic approach in a suspected case of RHD aims to:

- Identify the valvular lesion/s on the basis of clinical and investigational criteria **(Table 17.28)**.

TABLE 17.28: Common differentiating signs in various valvular lesions in RHD

Signs	*MR*	*MS*	*AR*
Peripheral signs			
Pulse	Nonspecific	Normal/low volume	Water hammer
Pulse pressure	Normal	Normal	Wide
Signs of aortic run-off	–	–	Present **(Table 17.27)**
Signs of CCF	Uncommon	Common	Uncommon
Signs of pulmonary edema	Uncommon	Common	Uncommon
Central signs			
Apex beat			
Location	Lateral and downward (LV)	Outward (RV)	Lateral and downward (LV)
Type	Heaving	Tapping	Hyperdynamic (ill-sustained)
Parasternal heave	–	Present	Present
Thrill	Pan systolic	Mid-diastolic	Early systolic
Diastolic shock	–	Present	–
First HS	Soft, muffled	Loud	Normal
Second HS	Wide split (early A_2)	Loud, wide split (late P_2)	Narrow split (late A_2)
Third HS	Present	–	–
Opening snap	–	Present	–
Organic murmur			
Type	PSM	MDM	EDM (decrescendo)
Location	Apical	Apical	Erb's area
Character	High pitched	–	High-pitched, blowing
Radiation	Towards axilla	–	Towards apex
Best heard in	–	Left lateral	Leaning forward
Flow murmurs	Apical EDM	EDM (*Graham Steell*)	Apical EDM (*Austin Flint*)
			PSM (Functional TR)
Investigations			
X-ray	LVH	RVH, Mitralization	LVH,
		PVH (Pulmonary plethora)	Prominent aortic knuckle
ECG	LVH	RVH/*P Mitrale*	LVH

- Exclude congenital lesions on the basis of age, past history of RF, absence of other congenital anomalies and other features **(Table 17.22)**.
- Exclude active RF and clinical carditis **(Table 17.24)** or sub-clinical carditis on the basis of echocardiography.
- Exclude or confirm the presence of complications CCF, infective endocarditis and arrhythmia on the basis of features discussed in respective chapters.
- Assess the severity of valvular defect and presence/severity of PAH to decide the need and time of surgery, as discussed earlier.

17.8 INFECTIVE ENDOCARDITIS

Infective endocarditis (IE) is an important cause of mortality and morbidity in children with pre-existing heart diseases, defined as the *infection of mural or valvular endocardium or endothelium of great vessels adjacent to heart (endarteritis).*

Etiology: *S. viridans* and *Staph. aureus* are leading causes of IE, though others, e.g. enterococci, gram negative organisms, e.g. Pseudomonas and fungal infections, e.g. *C. albicans* are emerging as important pathogens in partially-treated, immunocompromised or nosocomial cases.

Etiopathogenesis: IE is *extremely rare in normal heart*, with almost all cases having pre-existing CHD/RHD or post-operative nidus, e.g. Blalock-Taussig shunt or valvular prosthesis. IE is more common in VSDs, ToF, AS and AR and rare with PS, ASD and PDA.

Source of infection is usually a distant septic focus, e.g. dental, ENT or skin infections or surgical interventions, e.g. cardiac catheterization, genitourinary surgery or dental procedures. Cardiac infection generally begins at the site of damaged endocardium, where high-pressure jet of blood flow is directed. Hence, IE lesions are usually right ventricular in VSD, left ventricular in AR and over aortic endothelium in AS or coarctation of aorta. Localization of infection at affected site initiates inflammatory response with accumulation of fibrin and platelets, leading to formation of *vegetations*-the pathognomonic of IE. Vegetations in IE are typically small, friable and easily detachable to cause thromboembolic complications.

Clinically, IE presents as acute or subacute illness with:

- *Persistent fever* with chills and constitutional features, e.g. weight loss, anorexia and night sweats.
- *Cardiac signs of endomyocardial injury*, e.g.
  - New or changing murmurs
  - Cardiomegaly and/or refractory CCF
- *Peripheral signs of vasculitis*, e.g.
  - Splenomegaly
  - Moderate to severe anemia
  - Microscopic or gross hematuria
  - Clubbing and *splinter* hemorrhages over nails
  - Petechiae lesions over skin/mucus membranes
  - *Roth spots*-petechiae over retina
  - *Osler nodes*-tender erythematous nodules over finger pulp
  - *Janeway lesions*-non-tender erythematous patches over palm and soles
- *Signs of thromboembolic complications*, e.g.
  - Metastatic systemic abscesses in left-sided IE
  - Pulmonary embolism in right-sided IE.

Diagnosis of IE must be considered in any cardiac case with persistent unexplained fever, especially if the triad of *clubbing, splenomegaly and marked pallor* is present. It is confirmed by:

- *Blood cultures:* Since bacteremia in IE is low-grade and intermittent, preferably six or at least three samples of minimum 10 ml each, should be collected at ½ hourly interval for aerobic, anaerobic and fungal cultures. However, cultures are negative in ~50% cases, specially after partial antibiotic therapy and do not exclude IE.
- *Echocardiography* is extremely valuable to demonstrate vegetations or secondary lesions, e.g. ruptured chordae or perforated cusps, etc. LV lesions are better visualized (90%) than RV lesions (70%). However, small vegetations of <2 mm can be easily missed and a negative ECHO does not exclude IE.
- *Supportive investigations* include hemogram for normocytic, normochromic anemia, thrombocytopenia and raised ESR; as well as urinalysis for microscopic hematuria/albuminuria, which is present in >90% cases.

Duke criteria (1994) may be used to assist diagnosis of IE, based on the presence of—(a) any two major *or (b) one* major and 3 minor criteria or (c) five minor criteria. Diagnosis is considered as "possible" if only 1 major and 1 minor criteria or only 3 minor criteria are fulfilled.

- ***Major criteria*** include—(a) positive blood culture on at least two separate samples, and (b) echocardiographic evidence of intracardiac mass, abscess, prosthetic valve dehiscence or new valvular regurgitation.
- ***Minor criteria*** include—(a) *predisposing factor*, e.g. heart disease, (b) fever, (c) *immunological phenomena*, e.g. glomerulonephritis, arthritis, Osler nodes, Roth spots, etc. (d) *vascular phenomena*, e.g. major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions, etc., and (e) single positive blood culture or serologic evidence of infection.

Treatment: Early and appropriate, essentially intravenous, antimicrobial therapy in high doses for minimum

4–6 weeks is the mainstay of treatment in IE. Important steps in management of IE include:

a. ***Empirical therapy***, before the culture reports or in cases with negative cultures. Currently, drugs of choice for *native valve* IE is Ampicillin+Sulbactum (300 mg/kg/d Q4–6 hr) with *Gentamycin* (3 mg/kg/d q8hr) *for 4–6 weeks*. *Vancomycin* (40 mg/kg/d q8 hr) may be used in cases with penicillin allergy or suspected staphylococcal IE, along with Gentamycin and ciprofloxacin (20–30 mg/kg/d q12 hr).

   More intensive therapy is required in cases with prosthetic valves of 1 year with Vancomycin plus gentamycin plus cefepime plus Rifampicin.

b. ***Specific antimicrobial therapy*** is instituted after culture reports and sensitivity profile **(Table 17.29)**, which should continue for min 4–6 weeks.

c. ***Supportive therapy*** includes treatment of CCF, anemia and symptomatic management.

d. ***Surgical intervention*** is indicated in cases with ruptured aortic sinus, aneurysms, intractable CCF with severe valvular lesion (AR/MR) and failure of medical treatment.

Prevention: Antimicrobial prophylaxis **(Table 17.30)** prior to dental or other surgical procedures is essential to prevent IE in cases with heart disease, along with maintenance of good oral hygiene and early diagnosis and treatment of common infections.

IE prophylaxis is not recommended for ostium secundum ASD and mitral valve prolapse without regurgitation. After cardiac surgery or device closure, it is recommended only during first six post-operative months, unless residual lesion is present.

TABLE 17.29: Organism-specific drugs of choice in IE

Organism	*Antimicrobial agents (all IV)*
S. viridans/fecalis	Penicillin G + Gentamycin or
	Vancomycin* + Gentamycin
Staph. aureus	Cloxacillin + Gentamycin or
	Vancomycin* + Gentamycin
Staph. epidermidis	Vancomycin + Gentamycin
Gram -ve organisms	Ceftriaxone + Gentamycin
Fungal infections	Amphotericin + 5-flucytosine

*in penicillin allergic cases

TABLE 17.30: Antimicrobial prophylaxis for IE

- **Dental Rx/minor surgery** *(single dose 1 hour before Sx)*
  - PO Amoxycillin (50 mg/kg), or
  - PO Cephalexin or Cephadroxil (50 mg/kg)* or,
  - PO Azithromycin (15 mg/kg)* or
  - PO Clindamycin (20 mg/kg)*
- **Major surgery** *(2 doses — 1 hour prior and 6 hours after Sx)*
  - IV Ampicillin (50 mg/kg) + Gentamycin (1.5 mg/kg), or
  - IV Vancomycin* (20 mg/kg) + Gentamycin

* in penicillin-allergic cases

17.9 MYOCARDIAL DISORDERS

Myocardial disorders include two major groups—(a) acute myocarditis, (b) sub-acute or chronic cardiomyopathies, all characterized by *cardiac decompensation without organic murmurs (silent heart)*, though flow murmurs due to ventricular dilatation and functional valvular incompetence are common.

17.9.1 MYOCARDITIS

Myocarditis, i.e. the inflammation, necrosis or cytolysis of the myocardium, is a common cause of CCF and arrhythmias in children, occasionally leading to sudden unexplained death.

Etiology: *Viral infections* are predominant causes of myocarditis, apart other infections, connective tissue disorders and toxins **(Table 17.31)**. Viral myocarditis may develop either due to direct viral injury or as abnormal immune response to persistent viral infection.

Clinically, myocarditis usually presents with acute CCF, shock or arrhythmia, though few cases have a gradual course leading to dilated cardiomyopathy. History of preceding viral illness or signs of causative illness, e.g. rash or arthritis may be present.

Important clinical indicators include—(a) sudden unexplained hypotension/shock, (b) CCF refractory to usual therapy, and (c) cardiac signs, e.g. muffled heart sounds, gallop rhythm, arrhythmia and pansystolic

TABLE 17.31: Causes of myocarditis

- **Infections**
  - *Viruses:* Varicella, mumps, Coxsackie V
  - *Bacterial:* Diphtheria, Typhoid, Leptospirosis
  - Gram –ve sepsis *(acute toxic myocarditis)*
  - *Parasites:* Toxoplasmosis, Schistosomiasis
  - *Fungal:* Actinomycosis, histoplasmosis
  - *Rickettsiae:* Psittacosis
- **Connective tissue disorders**
  - Rheumatic fever
  - Rheumatoid arthritis
  - *Others:* SLE, Kawasaki disease
- **Toxins**
  - *Drugs:* Adriamycin, iron overload
  - Radiotherapy
  - Snake bite/scorpion sting
- **Miscellaneous**
  - *Nutritional:* Beri-beri
  - *IEMs:* Hurler syndrome, Pompe's disease
  - *Hematological:* Sickle cell disease
  - *Neuromuscular:* Friedreich ataxia, DMD

DMD: Duchenne muscular dystrophy; **IEM:** Inborn errors of metabolism

murmur due to dilatation of the valvular annulus and mitral incompetence.

Diagnosis is supported by—(a) *abnormal ECG finding*, e.g. low QRS voltage, ST segment/T wave changes, and prolonged QTc interval; (b) *biochemical evidence of myocardial injury*, e.g. raised CPK or LDH levels, (c) *chest X-ray* showing cardiomegaly with/without pulmonary edema and (d) poor myocardial function on *echocardiography*. Myocardial biopsy is confirmatory, but rarely needed.

Management of acute myocarditis aims towards its complications, e.g. CCF and shock, with—(a) bed rest and restricted activity, (b) oxygen or ventilatory support, (c) diuretics, and (d) inotropic agents, e.g. dopamine or dobutamine, to improve myocardial contractility.

Digitalization should be either avoided or done with half of the usual doses, as myocardium in these cases may be hypersensitive to digoxin with risk of arrhythmia.

Specific treatment is indicated in selected cases, e.g. prednisolone in rheumatic fever or IV immunoglobulins in Kawasaki disease, etc. Role of IVIG or corticosteroids in viral myocarditis is controversial.

Prognosis: Recovery depends on the cause and severity of myocardial injury. Important complications include-(a) arrhythmias. Which may cause sudden death and (b) cardiomyopathy-a long-term sequel.

17.9.2 CARDIOMYOPATHIES

Although myocardial functions are commonly impaired in congenital, valvular or coronary diseases, the term *cardiomyopathy (CM)* is used to denote rare primary diseases of the heart muscle, excluding abovementioned causes. Overall prevalence of cardiomyopathy is ~10 per lac live births.

Cardiomyopathies are broadly classified as:

- *Dilated or congestive CM*, the commonest type, with decreased contractility and consequent dilatation of ventricles.
- *Hypertrophic CM*, with inappropriate left ventricular hypertrophy, but normal ventricular contractility.
- *Restrictive CM*, with ventricular endocardial scarring and consequently reduced diastolic filling.

Dilated cardiomyopathy (DCM) is characterized by massive cardiomegaly involving all chambers, mainly LV. Decreased contractility of ventricles leads to stasis of blood flow and intracavitary thrombus formation. Histology reveals extensive foci of myocardial degeneration, necrosis and fibrosis, but *without* inflammatory cells.

Etiology: Though mostly *idiopathic*, DCM may be familial (20–50%), post-infectious or due to other causes **(Table 17.32)**.

TABLE 17.32: Causes of dilated cardiomyopathy

- *Idiopathic*
- *Inherited* disorders
  - Autosomal/XL/mitochondrial myopathies
  - Duchenne and other muscular dystrophies
  - Carnitine deficiency
- *Post-infectious:* Viral infections, diphtheria
- *Collagen disorders:* SLE, Kawasaki disease
- *Endocrinal:* Hypo/hyperthyroidism
- *Nutritional:* Beri-beri, selenium deficiency
- *Hematological:* Severe anemia, leukemia
- *Iatrogenic:* Adriamycin therapy, irradiation

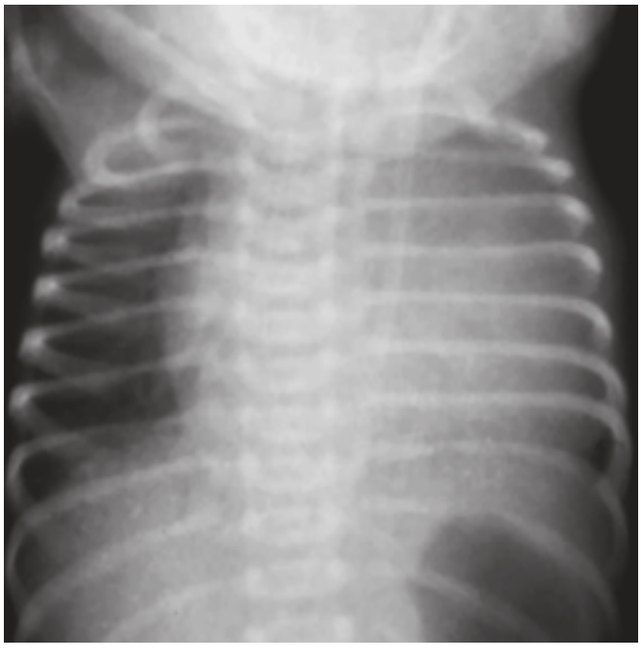


Fig. 17.23: Dilated cardiomyopathy.

Clinically, DCM presents at any age with variable manifestations, e.g. (a) asymptomatic cardiomegaly, (b) failure to thrive, (c) early signs of LVF, e.g. ill-sustained breast-sucking in infants or exertional dyspnea in older children, or (d) CCF, usually precipitated by mild infections or other stress.

Common cardiac finding include—(a) LV apical impulse, displaced outward and downward, (b) muffling of heart sounds (c) gallop rhythm, and (d) soft systolic murmur due to valvular ring dilatation (MR/TR).

Investigations: Chest X-ray reveals cardiomegaly with/without pulmonary edema **(Fig. 17.23)**. ECG may show sinus tachycardia, rhythm abnormalities, evidence of LVH with or without ST segment/T wave changes and features of LA or RA enlargement.

Echocardiography is diagnostic, with gross dilatation and poor contractility of ventricles, mainly LV. Pericardial effusion and intracavitary thrombus may be seen.

Cardiac catheterization, though rarely needed, demonstrates LV dysfunction, reduced cardiac output, valvular regurgitation and increased left-sided filling pressures.

Treatment is mainly supportive, with—(a) restriction of strenuous activity, (b) aggressive management of CCF with diuretics and digoxin, (c) after-load reduction with vasodilators, e.g. ACE inhibitors, (d) inotropic support with dobutamine/dopamine, and (e) anti-arrhythmic agents, if required. β-blockers have been found effective in some cases.

Anticoagulant therapy (coumadin or heparin) is indicated in cases with recurrent intraventricular thrombus formation. Cardiac transplantation is the only definite mode of therapy.

Prognosis: DCM is usually progressive, with complications, e.g. arrhythmia and thromboembolic episodes being terminal events.

Hypertrophic cardiomyopathy (HROM) is relatively uncommon, characterized by massive LVH but well-preserved contractile function. The ventricular cavity may be normal or small in size. Poor compliance of hypertrophied and fibrosed muscle leads to impaired diastolic ventricular filling, > LA enlargement, and > pulmonary venous congestion due to back-pressure. LV outflow obstruction may develop in few cases.

Histopathological features are typical, with gross disorganization of the muscle bundles (*Whorl pattern*), disorganized myofibrillar architecture and marked fibrosis.

Etiology: HROM is usually an autosomal dominant disease, involving mutations of the genes encoding cardiac β-myosin heavy-chain and myosin-binding protein C. Secondary HROM may develop in cases with LV outflow obstruction, e.g. coarctation of aorta/critical aortic stenosis and mucopolysaccharidosis.

Clinically, it is more common in adolescents and young adults, presenting with signs of reduced LV output, e.g. weakness, fatigue, exertional dyspnea, palpitation, dizziness, syncope and sometimes anginal pain due to coronary obstruction.

On examination: (a) Pulse is brisk due to the early systolic ejection of blood from the ventricle, (b) Apex beat is forceful, heaving and displaced laterally suggestive of LV pressure overload, and (c) Ejection systolic murmur is audible at the lower sternal border or apex, which increases in erect posture or during Valsalva maneuver (*unlike* most other murmurs, which usually reduce in intensity/duration on these activities).

Investigations: Chest X-ray shows mild LV cardiomegaly with normal pulmonary vasculature. ECG abnormalities include LVH, ST segment/T wave charges, deep Q waves and absent/diminished R waves in the left precordial leads.

Echocardiography is diagnostic, showing—(a) LVH encroaching the interventricular septum, (b) small LV cavity, and (c) narrowed LV outflow tract. *M-mode echo* demonstrates asymmetric septal hypertrophy of the interventricular septum and occasional systolic anti-motion of the anterior mitral valve leaflet.

Cardiac catheterization is useful before surgical intervention, to assess the LV compliance, presence of MR and dynamic LV outflow gradient.

Treatment can be medical or surgical.

Medical treatment includes—(a) avoidance of strenuous physical activity, (b) β-blockers, e.g. Propranalol to decrease anginal pain, arrhythmias and outflow obstruction, (c) calcium-channel blockers, e.g. nifedipine to improve diastolic filling and decrease hypercontractile systolic functions, (d) diuretics to reduce congestive symptoms, and (e) endocarditis-prophylaxis, prior to surgical interventions. *Digitalis is contraindicated and may increase the degree of obstruction.*

Surgical treatment, i.e. ventricular septal myotomy with/without mitral valve replacement is indicated in non-responsive cases with disabling angina/syncope or severe obstruction (pressure gradient > 50 mm Hg).

Periodic family screening with ECG/echocardiography is advisable even in asymptomatic siblings for early diagnosis of disease.

Prognosis is unpredictable and obstruction may be stable or slowly progressive. Common complications include arrhythmias and infective endocarditis.

Restrictive cardiomyopathy (RCM) is least common, characterized by impaired diastolic filling due to excessively rigid ventricular walls.

Etiology: RCM is usually secondary to hemosiderosis, hemochromatosis, endomyocardial fibrosis, hypereosinophilic syndrome and collagen vascular diseases, etc.

Clinically, exercise intolerance is the commonest presentation of RCM, as the cardiac output cannot be increased beyond a certain limit due to compromised ventricular filling. Other symptoms include weakness, dyspnea and chest pain.

Examination usually mimics constrictive pericarditis with raised JVP, pedal edema, hepatomegaly and *Kussmaul's sign*, i.e. paradoxical increase in JVP during inspiration.

Investigations: Chest X-ray is usually normal or reveals mild cardiomegaly and pulmonary venous hypertension. ECG may show the presence of atrial fibrillation or AV conduction defects.

Echocardiography is characteristic, revealing 'bi-atrial enlargement with normal cavity size of both ventricles'. LV systolic function is affected only in late stages.

Cardiac catheterization reveals characteristic "*square-root*" sign in the ventricular pressure recordings, with

reduced ventricular compliance and increased filling pressures.

Treatment: *Digoxin is not indicated as the systolic function is unimpaired.* Diuretics offer some benefit. Anticoagulants and antiplatelet agents may be used for prevention of thrombosis and a pacemaker may be used for management of complete heart block. Role of steroids and immunosuppressive agents is yet to be defined. Cardiac transplantation is an option, worth considering.

Endocardial Fibroelastosis

Endocardial fibroelastosis (EFE) is a rare cardiac disorder, pathologically characterized by white, opaque, fibroelastic thickening of the endocardium, usually involving LV.

Etiologically, EFE may be *primary* isolated abnormality or *secondary* to severe Left-sided obstructive CHD, e.g. aortic stenosis/atresia or coarctation of aorta. Although association is uncertain, *primary EFE has been associated with prenatal/postnatal mumps infection*.

Clinically, most cases present within first 6 months of life, with acute CCF following mild respiratory infection or with features of chronic heart failure, e.g. recurrent chest infections and failure to thrive.

Diagnosis is supported by—(a) cardiomegaly on X-ray, (b) LVH with strain pattern on ECG and (c) *bright appearing endocardial surface with poorly functioning LV* on echocardiography.

Treatment is mainly palliative, to control CCF with digitalis and diuretics. Most cases eventually succumb in early childhood unless heart transplant is possible.

17.10 ARRHYTHMIA

Spectrum of cardiac arrhythmia in childhood spans from common benign rhythm irregularities, e.g. premature or ectopic beats, to rare life-threatening arrhythmia, e.g. ventricular fibrillation. Major risk of any arrhythmia lies in significant drop in cardiac output, leading to syncope or progression to life-threatening arrhythmias with sudden death.

Clinical indicators: Cardiac arrhythmias are not uncommon in children, though many cases remain unrecognized. Presence of arrhythmia should always be suspected in a case with-(a) irregular heart beats, (b) disproportionate tachycardia/bradycardia, (c) unexplained/non-responsive CCF, (d) recurrent attacks of syncope, palpitation or chest pain, (e) family history of sudden deaths, and (f) past history of arrhythmia.

Etiology: Arrhythmia may be *congenital* with/without structural CHDs or *acquired* following—(a) rheumatic fever/heart disease, (b) myocarditis or myocardiopathies, (c) drugs, e.g. theophylline, digoxin, and (d) cardiac surgery.

TABLE 17.33: Cardiac arrhythmias in childhood

- **Benign and common abnormalities**
  - Sinus arrhythmia
  - Sinus bradycardia
  - Extra-systoles
  - Premature atrial/ventricular complexes
- **Tachy-arrhythmias**
  - Supraventricular tachycardia
  - Atrial flutter/fibrillation
  - Ventricular tachycardia
  - Ventricular flutter/fibrillation
  - Long Q-T syndrome
- **Brady-arrhythmias**
  - Sinus arrest/sinoatrial block
  - *AV blocks:* 1st, 2nd and 3rd degree
  - Congenital complete AV block
- **Sick sinus syndrome**
  - Bradycardia-Tachycardia syndrome

Classification: Arrhythmia may be broadly classified as: (a) benign rhythm irregularities, (b) tachyarrhythmias, (c) bradyarrhythmias, and (d) sick-sinus syndrome, i.e. alternating tachy-/brady-arrhythmias **(Table 17.33)**.

Salient features of important arrhythmias are discussed here with characteristic ECG changes in **Fig. 17.24**. For common antiarrhythmic agents *see* **Table 17.34**.

Sinus arrhythmia is accentuation of normal physiological variation with a slowing of heart rate (HR) during expiration and acceleration during inspiration. Sinus arrhythmia is common in preterms, febrile patients or drugs, e.g. digoxin therapy. It is usually abolished by exercise.

Sinus bradycardia denotes HR <90 in newborns or <60 in older children. It is common in athletes and myxedema and needs to be differentiated from SA block or AV block. Children with sinus bradycardia are able to increase their HR >100 with exercise, unlike those with SA/AV blocks.

Extrasystoles indicate discharge from an ectopic focus in atrial, junctional or ventricular tissues, i.e. other than SA node. Isolated extrasystoles are of no significance, unless associated with underlying heart disease or digoxin therapy.

Premature atrial complexes (PAC), characterized by presence of P waves with normal, prolonged or absent QRS complexes and *without compensatory pause* are common, even in normal children.

Premature ventricular complexes (PVC) are characterized by premature, wide and bizarre QRS complexes, often associated *with compensatory pause*. When frequent, PVCs may assume a definite rhythm, i.e. *bigeminy* (alternating with normal beats) or *trigeminy* (after two normal beats). Although benign PVCs are common in anxiety, febrile illnesses and stimulant drug therapy, presence of two or more consecutive PVCs *or* increased frequency after exercise indicates potential risk of

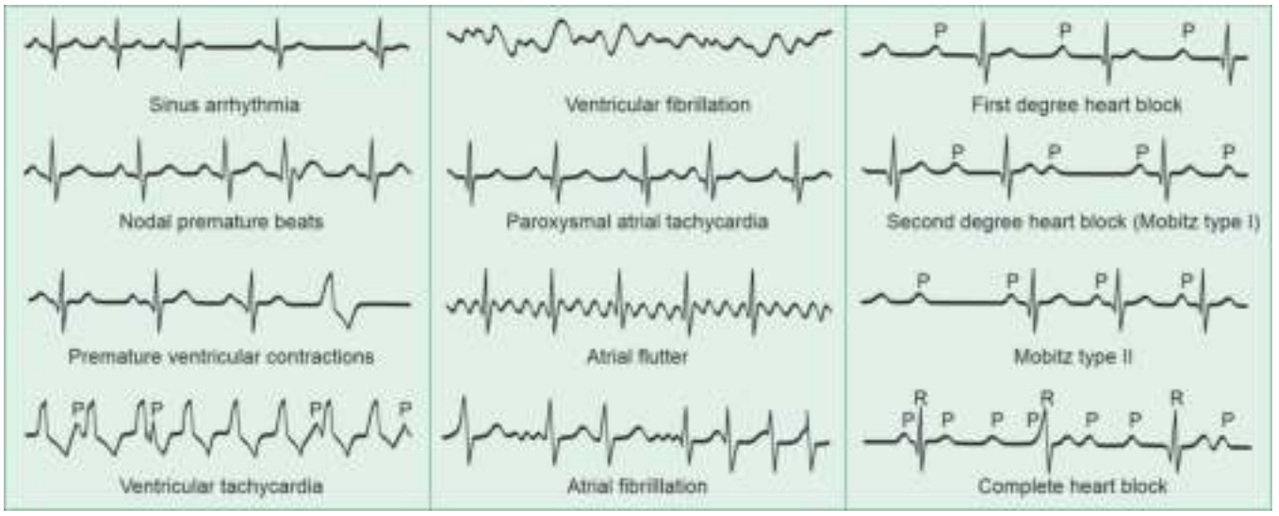


Fig. 17.24: ECG changes in common arrhythmia.

degeneration into more severe arrhythmia. IV Lidocaine is drug of choice in these cases.

Supraventricular tachycardia (SVT) or *paroxysmal atrial tachycardia* (PAT) is characterized by abrupt onset and cessation of severe tachycardia (>180–220/min), originating proximal to the bifurcation of the bundle of His due to an abnormal mechanism (specifically excluding sinus tachycardia).

Etiologically, SVT is usually associated with—(a) acute infection, (b) use of sympathomimetic drugs, e.g. decongestants, or (c) underlying heart disease in 20% cases, e.g. Ebstein anomaly.

Pathophysiologically, SVT may be caused by—(a) re-entry of a premature atrial wave back into atrium due to refractory AV node (*echo beats*) using an accessory pathway (commonest type in 90% cases), (b) re-entry without accessory pathway and (c) ectopic or automated tachycardia.

Re-entry SVT are further classified as atrioventricular reentry tachycardia (AVRT) or atrioventricular nodal reentry tachycardias (AVNRT).

Clinically, while short episodes are well tolerated except palpitation, prolonged attacks may lead to CCF. Infants may present with feeding problems, irritability and shock.

ECG changes are often limited to tachycardia and narrow QRS complexes during the attack, but may show typical features of *Wolff-Parkinson-White syndrome*, i.e. short PR interval with slow upstroke of QRS complex (*delta wave*). A 12-lead ECG is essential before starting the treatment, while 24-hour ECG (Holter monitoring) is necessary to detect brief and asymptomatic attacks.

Treatment of SVT includes:

- Abolition of acute attack by
  - Vagal stimulation by immersion in ice-cold water, Valsalva maneuver, breath-holding, etc.
  - Drugs, e.g. IV adenosine* (drug of choice; 50–300 mg/kg bolus) followed by propranolol, etc., to prevent the recurrence.
  - Synchronized DC cardioversion
- Maintenance therapy with digoxin, propranolol or verapamil.
- Radio-frequency ablation of accessory pathway.

*Adenosine has a very short half-life of <10 seconds and should be given as a rapid bolus through a large vein near the heart, (e.g. antecubital fossa) flushed immediately with 5 ml normal saline. Begin with the first bolus of 100 µg/kg and repeat every 2 minutes in incremental doses till response or maximum dose of 500 µg/kg (300 µg/kg in newborns) is reached. Patient should be simultaneously monitored by ECG.

Prognosis for complete resolution of SVT depends on age of onset and etiology. SVT diagnosed in infancy is likely to resolve in 70–80% as compared to only in 33% patients diagnosed after 1 year of age.

Atrial flutter presents with regular or regularly irregular tachycardia (HR: 250–400/min), due to a *micro-reentrant* loop in atrial tissue and some form of anatomical obstruction/discontinuity in conduction passage, e.g. fibrosis, valve annulus, etc.

It is most commonly seen in cardiac cases with dilated atria, e.g. rheumatic MS, tricuspid atresia or Ebstein anomaly. Diagnosis is confirmed on ECG with rapid and regular *saw-toothed flutter waves*. DC cardioversion is the treatment of choice in emergency, followed by digoxin therapy, with/without quinidine or procainamide for long-term control.

Atrial fibrillation is rare in children, presenting with very rapid and chaotic atrial excitation, i.e. fibrillatory waves (300–700/min) and irregularly irregular ventricular response. It may develop in conditions producing atrial flutter or after cardiac surgery. Digitalization, followed by DC cardioversion or quinidine therapy is the treatment of choice.

TABLE 17.34: Antiarrhythmic agents at a glance

Drugs	*Indications*	*Dose*	*Side-effects*
Ia: Na^+ fast channel inhibitor, prolong repolarization			
Quinidine	SVT[1], AFl, AFb, VPC	PO 20–60 mg /kg/d q6h	Heart blocks, proarrhythmia, gastritis, hemolysis
Procainamide	SVT[1], AFl, AFb, VPC	IV 3–6 mg/kg (L) > 20–80 µg/kg/min PO 15–50 mg/kg/d q6h	Heart blocks, proarrhythmia, blood dyscrasia, lupus
Disopyramide	SVT[1], AF, AFb, VPC	PO 10–25 mg/kg/d q6hr (half the dose >10 yr)	Heart blocks, proarrhythmia, anti-cholinergic effects
Ib: Na^+ Fast channel inhibitor, shorten repolarization			
Lidocaine	VPC, VT[2], VFb[3]	IV 1–2 mg/kg (L) >20–50 µg/kg/min	Heart blocks, seizures, coma
Mexilitene	VT, VPC, ? LQTS	PO 6–15 mg/kg/d q24h	Rash, GIT upset
Phenytoin	Digitalis-induced arrhythmia	PO 3–6 mg/kg/d q12h IV 10–15 mg/kg slowly	Gingival hyperplasia, neurotoxicity
IC: Na^+ channel inhibitors			
Flecainide	SVT, VT	PO 3–10 mg/kg/d q8hr	Blurred vision, proarrhythmia
Propafenone	SVT, AFb, VT	PO 150–300 mg/m^2/d q8hr	hypotension, hepatotoxicity
II: Beta-blockers			
Propranolol	SVT[1], PVC, LQTS	PO 1–4 mg/kg/d q6h	Heart blocks, bronchospasm, hypotension
III: Prolong repolarization/refractory period			
Amiodarone	Resistant/Refractory SVT, JET, VT	IV 2–5 mg/kg L >5–15 µg/kg/min PO 5–10 mg/kg/d q12h	Thyroid dysfunction, Hepatotoxicity, pulmonary fibrosis *C/I: severe sick sinus disease/AV block without pacemaker*
Bretylium	VT, VFb	IV 5 mg/kg/dose q20 min till response > q6h	Hypotension/bradycardia
IV. Miscellaneous			
Digoxin	SVT[1], AF, AFb	PO 10 µg/kg/d q12hr (IV: 3/4th PO dose)	Ectopics, heart blocks, GIT upset
Verapamil (Ca^{++} channel blocker)	SVT[1]	IV 0.1–0.2 mg/kg/dose q20 min two times PO 2–7 mg/kg/d q8h	Heart blocks, hypotension/CCF *C/I: VT, AFb, severe CCF* *Not for use in infants*
Adenosine (Purinergic agonist)	SVT[1]	IV 50–300 µg/kg/dose[4]	Heart blocks/ectopics

Note: All IV anti-arrhythmic agents should be infused slowly except adenosine (*see* below) with constant BP and ECG monitoring.
[1]If no response to vagotonic maneuvers. Use DC cardioversion in critically-sick patients. [2]Cardioversion is preferred choice. [3] Defibrillation is preferred choice. [4]Extremely short-acting, start with 50 mg/kg/dose and repeat every 2 min with increasing doses by 50–100 mg/kg till response.
SVT: Supraventricular tachycardia; **VPC:** Ventricular premature contractions; **PVC:** Premature ventricular complexes; **AFl:** Atrial flutter; **AFb:** Atrial fibrillation; **VT:** Ventricular tachycardia; **VF:** Ventricular fibrillation; **LQTS:** Long QT syndrome; **JET:** Junctional ectopic tachycardia

Ventricular tachycardia, defined as *at least 3 PVCs at HR >120/min*, is less common than SVT in children. It may be paroxysmal or incessant, associated with myocarditis/cardiomyopathies, anomalous origin of coronary arteries, long QT syndrome, cardiac tumors and post-cardiac surgery. IV lidocaine is the drug of choice along with correction of hypoxia and dyselectrolytemia.

Ventricular fibrillation is a potentially fatal arrhythmia (due to above causes) that results in death unless rapidly corrected. Although a thump on chest may be useful in emergency, external cardiac massage and DC defibrillation is the treatment of choice.

Long QT syndrome (LQTS) is a rare cause of recurrent syncopal attacks and sometimes sudden death due to a malignant ventricular arrhythmia—*torsades de pointes*. Nearly 50% cases are familial, with abnormalities in cardiac Na^+/K^+ channels. Diagnosis is based on:

- history of unexplained and recurrent syncopal attacks,
- typical ECG findings with QTc interval >0.47 and
- family history of sudden death or LQTS.

Treatment includes β-blockers to blunt the HR response to exercise and use of pacemakers.

Atrioventricular (AV) blocks, the commonest brady-arrhythmia, may be divided into:

- ***1st degree heart block***, i.e. prolonged PR interval but all atrial impulses are conducted to ventricle.
- ***2nd degree heart block,*** where some atrial impulses are not conducted to ventricle. It includes:
  - *Wenckebach type or Mobitz type I*, with constant PP interval but PR interval increasing progressively till a dropped beat. The ensuing PR interval is again normal and cycle is repeated.
  - *Mobitz type II*, where occasional atrial beat is not conducted to ventricle.
- ***3rd degree or complete heart block,*** where no atrial impulse is conducted to ventricle.

Complete heart block may be congenital or acquired. Congenital complete heart block is common in babies born to mothers with SLE or other connective tissue disorders. Acquired heart blocks may develop in—(a) complex CHDs, (b) myocarditis, (c) after cardiac surgery.

Clinically, these cases may be asymptomatic or present with attacks of dizziness or syncope (*Stokes-Adams syndrome*), Cannon waves on JVP due to contraction of atria against a closed tricuspid valve(AV discordance), CCF/cardiomegaly, and occasionally sudden death.

Diagnosis is confirmed on ECG, i.e. absence of constant relationship between P waves and QRS complexes.

Treatment: Cardiac pacing with permanent pacemaker is needed *only* in symptomatic cases with recurrent syncopes, HR <40 and cardiomegaly. Otherwise, prognosis is favorable even in untreated cases.

Sick sinus syndrome is characterized by intermittent or alternating attacks of tachycardia and bradycardia, causing palpitation and syncopal attacks. It is most commonly seen after cardiac surgery, though occasionally may also develop in normal children without cardiac disease. Treatment includes insertion of a demand-driven ventricular pacemaker along with drugs to control tachyarrhythmias, e.g. propranolol, quinidine, etc.

17.11 PERICARDITIS

Pericarditis denotes infective or non-infective inflammation of the pericardium, which may or may not be associated with excess fluid collection in pericardial sac *(pericardial effusion)*, secondary compression of heart with compromised filling (*constrictive pericarditis*) or severe limitation of cardiac output (*cardiac temponade)*. Normal pericardial sac contains ~10–15 ml of serous fluid as shock absorber and lubricant.

Etiopathogenesis: Tuberculosis is the commonest cause of exudative pericardial effusion in India, followed by bacterial infections, e.g. *Staph. aureus* (pyopericardium). Infection may reach pericardium by direct spread from neighboring foci, e.g. pneumonia, empyema, osteomyelitis of ribs, etc. or via hematogenous spread from a distant foci, e.g. meningitis.

Transient pericardial effusion is common in viral infections (? hypersensitivity), while collagen disorders are usually associated with large effusions and polyserositis in older children **(Table 17.35)**.

Pathophysiology: Depending on the cause, pericardial fluid may be serous, fibrinous, purulent or hemorrhagic. Except in small serous effusions, rising intra-pericardial pressure due to accumulated fluid affects cardiac functions and may cause *cardiac tamponade*, characterized by progressive limitation of the ventricular diastolic filling and reduction in stroke volume. In most cases, the effusion resolves spontaneously or on treatment. However in some cases (specially tuberculosis), gradual organization and fibrous thickening of pericardium may lead to obliteration of the pericardial space, i.e. *constrictive pericarditis*.

TABLE 17.35: Causes of pericarditis

- **Infective**
  - *Bacterial:* Staphylococci, streptococci, pneumococci
  - Tuberculosis
  - *Viral:* Coxsackie B, EBV, adenovirus
  - *Parasitic: E. histolytica*, hydatid disease
  - *Fungal:* Histoplasmosis, actinomycosis
- **Inflammatory**
  - Rheumatic fever
  - *Collagen disorders:* Rheumatoid arthritis, SLE
- **Hematological:** Leukemia, bleeding diathesis
- **Traumatic chest injuries** (hemopericardium)
- **Iatrogenic:** Post-pericardiotomy, radiotherapy
- **Others:** Uremia, hypothyroidism
- **Idiopathic**

Clinical manifestations depend upon the amount, type and rapidity of fluid collection. Small effusions may be completely asymptomatic.

Common presenting symptoms include—(a) dull or stabbing pre-cordial or left-shoulder pain due to diaphragmatic/pleural irritation, which aggravates on supine position and relieves on sitting and leaning forward, (b) cough, dyspnea, dysphagia and hiccough due to bronchial, esophageal or phrenic nerve compression, (c) constitutional symptoms, e.g. fever, weight loss, etc. or (d) features of primary disease. Physical findings depend on whether the pericarditis is associated with effusion or cardiac tamponade.

- ***Pericarditis with minimum effusion*** presents with *Pericardial friction rub* — a scratching, grating, high-pitched sound, best heard with the diaphragm of stethoscope applied firmly at the lower left sterna border in sitting and leaning-forward position. Friction rub disappears with increasing fluid collection.
- ***Moderate effusion without cardiac tamponade*** is characterized by—(a) quiet pericardium with ill-defined apical impulse, (b) cardiomegaly on percussion with cardiac dullness extending beyond the apex beat, (c) muffling of the heart sounds, and (d) peripheral signs of poor diastolic filling, e.g. tachycardia, raised JVP, congestive hepatomegaly and basal lung crepitations.
- ***Cardiac tamponade or constrictive pericarditis*** presents with severe peripheral signs due to poor diastolic filling, e.g. (a) low volume pulse with *pulsus paradoxus*, (b) distended neck veins with *Kussmaul's sign*-paradoxical increase in JVP during inspiration, (c) tender, congestive hepatomegaly, and (d) hypotension due to compromised cardiac output.

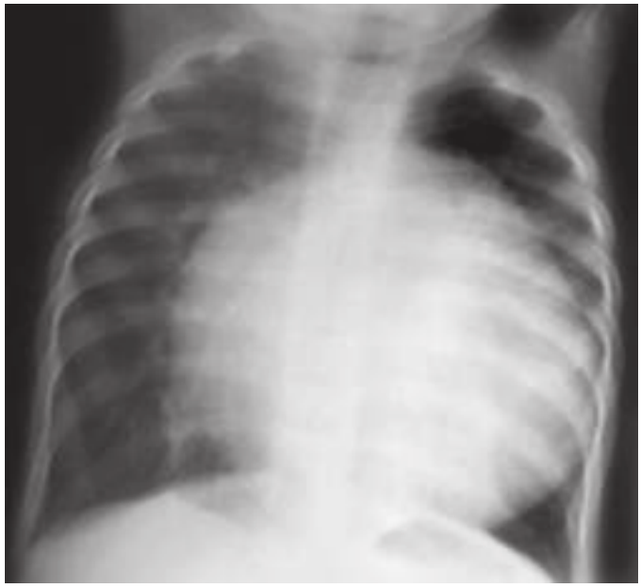


Fig. 17.25: Pericardial effusion.
Note: Narrow cardiac pedicle and oligemic lung fields

Diagnosis: USG is the best method to detect very small pericardial effusions, while in others, diagnosis is supported by:

- *Chest X-ray showing* cardiomegaly with narrow pedicle due to compression of great vessels, i.e. *Pear-shaped heart and oligemic lung fields* (d/d CCF with usually plethoric lung fields). However, heart size is reduced in constrictive pericarditis **(Fig. 17.25)**.
- *ECG with*-(a) low-voltage QRS complexes due to dampening effect of pericardial fluid, (b) elevated ST segment due to myocardial irritation, and (c) inverted T waves due to myocardial inflammation.
- USG is diagnostic, revealing presence of an echo-free space between the epicardium and pericardium. Presence of both, anterior as well as posterior effusions, indicates large effusions.
- *Echocardiography* is useful to detect impending cardiac tamponade/constrictive pericarditis, indicated by—(a) flattening of septal motion, (b) collapse of RA in late diastole, and (c) collapse or indentation of RV free wall (specially outflow tract) in diastole.
- *Pericardiocentesis* with biochemical analysis (exudate *vs.* transudate) and culture of aspirated fluid is necessary for etiological diagnosis. On gross appearance, pericardial fluid is—(i) *Xanthochromic* in tubercular pericarditis, (ii) *Thick purulent* in bacterial infections, e.g. *Staph. aureus,* (iii) *Serofibrinous* in viral or rheumatic pericarditis and connective tissue disorders, and (iv) *hemorrhagic* in malignancy, trauma and bleeding disorders.
- *Relevant investigations* for etiological diagnosis, e.g. tuberculin test, ASO titers, etc.

Management of pericardial effusion depends on primary etiology and includes:

- *Specific treatment*, e.g. antibiotics in pyopericardium; antitubercular drugs plus steroids in tubercular effusions; and steroids in rheumatic fever or collagen disorders.
- *General supportive measures*, e.g. bed rest, oxygen, analgesics, and nutritional support. Decongestive therapy with diuretics and digoxin should be avoided due to risk of further compromise in cardiac output.
- *Surgical interventions*, i.e. pericardiocentesis is indicated in pyopericardium or cardiac tamponade. Constrictive pericarditis requires decortication of pericardium with radical pericardiectomy.

17.12 CHILDHOOD HYPERTENSION

Systemic hypertension in childhood is defined as *the systolic or diastolic blood pressure (SBP/DBP) exceeding 95th percentile for age, sex and height-specific normal values on at least three occasions, 1–3 weeks apart for children < 13 years.*

Table 17.36 defines and classify severity of hypertension in children according to the latest American Academy of Pediatrics (AAP) Guidelines 2017, based on age, sex and height related norms, which can be obtained using the calculator available at *https://www.mdcalc.com/calc/4052/aap-pediatric-hypertension-guidelines.*

Prevalence of hypertension in all pediatric age groups is estimated to be ~2–5%. Unlike adults, over 90% cases of hypertension in children are secondary and need thorough diagnostic workup to identify underlying cause. However in recent years, primary or idiopathic hypertension is being increasingly recognized in obese adolescents (~15–20%).

Etiology: Renal or renovascular disease is the leading cause of childhood HT, whether transient or permanent. While >90% of cases with transient hypertension are due to post-streptococcal glomerulonephritis **(Table 17.37)**, chronic renal diseases are responsible for ~3/4th cases of persistent hypertension **(Table 17.38)**.

Family history is common in cases of primary hypertension with possible multifactorial etiology involving genetic and environmental factors.

Clinical manifestations of hypertension depend on its severity, chronicity and underlying cause. Essential hypertension in children is usually mild and asymptomatic, detected on routine examination. Secondary hypertension may present with features of:

- *Underlying causes*, e.g. renal disease (growth failure, edema, abdominal mass), vascular disease (unequal peripheral pulses, bruits) adrenal disease (obesity, virilization) or tumors (weight loss, abdominal mass), etc.
- *Intracranial* hypertension, e.g. headache, vomiting, dizziness, etc. or *hypertensive encephalopathy*, e.g.

TABLE 17.36: Definition and severity of childhood hypertension

Category	*Age <13 years*	*Age>13 years*
Normal	<90th percentile	<120 /<80 mm Hg
Elevated BP	>90-<95th percentile	120–129 /<80 mm Hg
Stage I hypertension	>95th percentile*	130–139 / 80–89 mm Hg
Stage II hypertension	>95th percentile + 12 mm Hg	>140/90 mm Hg

*but less than stage II hypertension (>95th>95th percentile + 12 mm Hg)

TABLE 17.37: Causes of transient hypertension

Renal causes
- Acute glomerulonephritis
- Hemolytic-uremic syndrome
- Acute pyelonephritis
- Renal trauma/surgery

Neurological causes
- *Raised ICP:* Encephalitis
- Guillain-Barré syndrome
- Poliomyelitis

Others:
- *Drugs:* Steroids, sympathomimetics
- *Dyselectrolytemia:* Hypernatremia, hypercalcemia

TABLE 17.38: Causes of persistent hypertension

- **Renal causes (>75%)**
  - Chronic glomerulonephritis (~ 40%)
  - Chronic pyelonephritis (~ 25%)
  - Congenital anomalies, e.g. polycystic kidney*
  - Obstructive uropathy*/vesicouretric reflux
  - Renal tumors
  - Connective tissue disorders, e.g. SLE, HSP
- **Reno-vascular (10–20%)**
  - Renal artery stenosis*
  - Renal vein thrombosis*
- **Vascular (2–3%)**
  - Coarctation of aorta*
  - Aorto-arteritis
  - Vasculitis syndromes: Henoch-Schönlein purpura
- **Endocrinal (<1%)**
  - Cushing syndrome, congenital adrenal hyperplasia
  - Hyperaldosteronism
  - Pheochromocytoma
  - Neural-crest tumors, e.g. neuroblastoma
- **CNS disorders (<1%)**
  - ↑*ICP:* Brain tumors, hydrocephalus
  - Familial dysautonomia
- **Essential or idiopathic (<10%)**

*Common causes in newborns and early infancy

altered sensorium, seizures, neurological deficits, diplopia and fundal changes.
- *Cardiovascular stress*, e.g. epistaxis, cardiomegaly, CCF or renal failure.

Fundus examination is essential in all cases and important retinal changes in hypertension include: (a) generalized constriction of arterioles, (b) retinal edema, (c) flame-shaped hemorrhages, (d) cotton-wool spots denoting retinal infarcts, and (e) papilledema. Features of long-standing hypertension, e.g. thick vessels with *silver-wire or copper-wire appearance* are rare in children.

TABLE 17.39: Screening cut-offs for hypertension (AAP2017)

Age Yrs	*Boys*		*Girls*	
	SBP	*DBP*	*SBP*	*DBP*
1	98	52	98	54
2	100	55	101	57
3	101	58	102	60
4	102	60	103	62
5	103	63	104	64
6	105	66	105	67
7	106	68	106	68
8	107	69	107	69
9	107	70	108	71
10	108	72	109	72
11	110	74	111	74
12	113	75	114	75
≥13	120	80	120	80

Diagnosis of hypertension involves a two-step process—(a) confirming its presence, and (b) etiological diagnosis.

Step I. Screening and confirmation of hypertension requires repeated BP measurements as follows:
- All children > 3 years of age should undergo annual BP measurement, more frequently if are at-risk for essential hypertension (family history, obesity) or have systemic illnesses known to cause secondary hypertension. Children <3 years also need regular BP measurements, if are at risk for secondary hypertension.
- Automated BP measurement devices work on oscillometric principle and tend to overestimate BP. These devices can be used for screening purpose but abnormal values must be confirmed manually by *auscultatory method*. As mercury-based sphygmomanometers are being phased out due to environmental concerns, a digital or aneroid device may be used.
- AAP guidelines 2017 also provide for age-and sex-related cut-off values for screening BP in children of median stature **(Table 17.39)**, to identify children who need detailed evaluation.
- BP should be recorded in comfortable setting in right arm, with appropriate cuff-size (bladder width ~ 40%

and bladder length ~80–100% of arm circumference). Normally, a cuff size of 4×8 cm, 6×12 cm, 9×18 cm and 10×24 cm is required for newborn, infant, child and adolescent, respectively. Child must be asked to rest for 5–10 minutes before taking BP and at least 2 reading must be recorded during each occasion.

- BP should be recorded by '*auscultatory method*', with appearance of first Korotkoff sound as indicator of systolic BP and fifth Korotkoff sound (or muffling of fourth Korotkoff sound) as indicator of diastolic BP. In infants, BP may be recorded by Doppler or '*flush method*'.

  Flush method is useful to determine the average of systolic and diastolic BP. The limb is elevated above the couch till the distal part appears blanched due to drainage of blood. A cuff is then applied to the wrist/ankle and pressure is elevated above the expected systolic pressure. When deflated slowly (5 mm Hg/second), the pressure at which the hand/foot appears flushed indicates average pressure.
- At least three readings on different occasions, minimum one week apart (except in very severe cases) should exceed 95th percentile for diagnosis of hypertension (>90th percentile for diagnosis of elevated BP).
- Ambulatory BP monitoring is recommended in cases with elevated blood pressure category for >1 year or stage 1 hypertension on three clinical visits.
- In hypertensive children, BP should also be recorded in lower limbs. Normal BP in lower limbs is 10–15 mm Hg higher than in upper limbs, due to more muscle mass and peripheral resistance. In coarctation of aorta or aortoarteritis (Takayasu disease), BP in lower limbs is normally less than in upper limbs.

Step II. Etiological diagnosis depends on—(a) detailed history and review of earlier case records, whether hypertension is transient or persistent, (b) physical examination for features of causative disease and (c) relevant investigations **(Table 17.40)**, depending on probable etiology. Plasma renin activity (PRA) is a useful basic investigation in unexplained hypertension that differentiates renal or renovascular hypertension (increased PRA) from other causes (normal PRA).

Children with primary hypertension are usually older than >6 years, overweight, have a family history of hypertension and have no obvious cause of secondary hypertension. They should also be screened for HbA_1C, lipid profile, serum creatinine and liver enzymes.

Echocardiography is recommended in all cases to assess the target organ damage, before starting pharmacotherapy.

Management of hypertension aims to keep the BP consistently <90th percentile, by (a) Specific antihypertensive therapy, (b) Treatment of underlying cause, e.g. surgical intervention in correctible renal, vascular or neoplastic disorders and (c) non-pharmacological methods, e.g. salt-restricted diet, weight reduction and exercise, which are more useful in essential than secondary HT and hence, of limited value in children.

TABLE 17.40: Investigations in a hypertensive child

Base-line investigations
- Urinalysis sp. for hematuria, proteinuria
- Renal function tests, e.g. BUN, creatinine
- S. electrolytes
- Renal USG sp. for cong. anomalies, obstructive uropathy
- X-ray chest sp. for pulmonary edema, notching of ribs
- ECG sp. for LVH, ECHO for CoA
- **Selective investigations**
- ***Suspected renal or renovascular cause:***
  - Plasma renin activity (PRA)
  - ASLO, C3 for acute nephritis
  - Uroimaging studies, e.g. IVP, MCU, renal scan
  - Renovascular studies, e.g. Doppler, angiography
  - Renal biopsy
- ***Suspected vascular disease***
  - Aortography/digital substraction angiography
  - P-ANCA and c-ANCA for vasculitis
- ***Suspected endocrinal cause:***
  - Urine/plasma catecholamines (Pheochromocytoma)
  - MIBG scan, CT/MRI (Neuroblastoma)
  - Cortisol challenge tests (Cushing syndrome)
  - Urinary 17-OH/ketosteroids (Cong. adrenal hyperplasia)
  - S. aldosterone (Hyperaldosteronism)

Many anti-hypertensive agents are available for pediatric use **(Table 17.41)** and the choice depends on the cause and severity of hypertension. Continuous BP monitoring is necessary to modify the choice of drug, route of administration and their dosage/frequency. Diuretics are needed in almost all cases. Some special considerations in hypertensive therapy are as follows:

- ***Hypertensive crisis/encephalopathy*** is a serious medical emergency that needs aggressive, quick-acting antihypertensive therapy with IV sodium nitroprusside (0.5–0.8 µg/kg/min) or IV Labetalol (0.2–2.0 mg/kg/hour) or IV Esmolol (100–500 µg/kg/min) or IV Nicardipine (1–3 µg/kg/min) along with diuretics. Less severe cases may be managed with sublingual/oral Nifedipine. Other drugs like IV hydralazine or diazoxide are no longer preferred in hypertensive crisis. Rapid reduction of BP in hypertensive crisis may worsen the critical organ perfusion and should be avoided.
- ***Hypertension due to renal disease*** is usually associated with high plasma renin activity, and hence, best treated with ACE-inhibitors, e.g. captopril or enalapril, along with diuretics. Calcium channel blockers, e.g. amlodipine and β-blockers, e.g. Propranolol may also be used in these cases. *ACE inhibitors should be avoided till renovascular cause is ruled out.*
- ***Hypertension due to neural crest tumors***, e.g. neuroblastoma or pheochromocytoma, is usually associated

TABLE 17.41: Commonly used antihypertensive drugs in children

	Drug	*Dosage*	*Side-effects*
Diuretics			
Hydrochlorothiazide	PO	1–2 mg/kg/dose (Q12hr)	Hypokalemia, hyperuricemia
Furosemide	PO/IV	1–2 mg/kg/dose (Q6hr)	Hypokalemia
Bumetanide	PO	0.01–0.1 mg/kg/dose (Q6–24hr)	Hypokalemia, hyperuricemia
Arteriolar – vasodilators			
Hydralazine	IV	0.1–0.5 mg/kg/dose (Q2–4hr)	Tachycardia, drug induced lupus
	PO	0.25–1 mg/kg/dose (Q6–8hr)	
Diazoxide	IV	1–5 mg/kg/dose	Hyperglycemia, hypotension
Sodium nitropruside	IV	0.5–8.0 µg/kg/min	Thiocynate poisoning
Reserpine	IM	0.07 µg/kg/dose (Q8hr)	Nasal stuffiness, hypotension
α-Adrenergic blockers			
Phentolamine	IV	0.05–0.1 mg/kg/dose (Q1–2hr)	Reflex tachycardia
Phenoxybenzamine	IV	0.1–0.6 mg/kg/dose (Q8–12hr)	Arrhythmia
Prazocin	PO	0.005–0.1 mg/kg/dose (q6–12hr)	Orthostatic hypotension
β-blockers			
Propranolol	IV	0.01–0.1 mg/kg/dose	Bronchospasm
	PO	0.25–1.0 mg/kg/dose (Q6–8hr)	
Atenelol	PO	1–2 mg/kg/dose (Q24hr)	Bronchospasm
Labetelol	IV	0.2–2 mg/kg/hour (titrate)	Bronchospasm, hypotension
Esmolol	IV	50–300 µg/kg/min	Bronchospasm, hypotension
Renin-angiotensin inhibitors			
Captopril	PO	0.1–0.5 mg/kg/dose (Q8–12hr)	Proteinuria, rash, neutropenia
Enalapril	PO	0.1 mg/kg/dose (Q12–24hr)	Hypotension
Enalaprilat	IV	0.005–0.010 mg/kg/dose slowly.	Hypotension
Ca^{++} channel blockers			
Nifedipine	SL/PO	0.2–0.5 mg/kg/dose (Q4–6hr)	Facial flushing, tachycardia
Verapamil	PO	1–2 mg/kg/dose (Q8hr)	
Nicardipine	IV	1–3 µg/kg/min	Hypotension, headache
Amlodipine	PO	0.1–0.6 mg/kg/dose (Q24hr)	Edema, flushing
Sympathomimetic agents			
α-Methyldopa	IV	5–10 mg/kg/day slow drip or	Sedation hepatotoxicity
		2.5–5.0 mg/kg/dose (Q6–12hr)	Positive Coombs' test
Clonidine	PO	3–5 µg/kg/dose	Sedation, rebound hypertension

with sympathetic overactivity and hence, best treated with combination of an α-blocker, e.g. phentolamine or Prazosin and a β-blocker, e.g. Atenolol or Labetalol.

- ***Primary hypertension or persistent hypertension due to uncorrectable causes*** needs a step-wise approach to achieve sustained control, starting with—(a) non-pharmacological measures and diuretics in mild cases, (b) addition of an ACE-inhibitor or β-blocker in more moderate cases, and lastly, (c) multi-drug therapy with β-blockers, ACE-inhibitor and calcium-channel blocker, e.g. amlodipine. Centrally acting clonidine or β-blocker Prazosin are rarely used in refractory cases. Number of drugs, their doses and frequency needs to be frequently modified, depending on the control of BP.

American Academy of Pediatrics guidelines (2017) recommends a step-wise approach for management of primary or essential hypertension **(Table 17.42)**.

Prognosis of secondary HT depends upon the underlying cause, duration/severity, and response to specific therapy. While hypertensive encephalopathy and LVF are common causes of immediate mortality, persistent moderate HT may lead to secondary organ damage after many years, e.g. cardiomyopathy, retinopathy

TABLE 17.42. Step-wise management of hypertension*

	Elevated BP	*Stage I HTN*	*Stage II HTN*
Step I	LSM > BP after 6 mo	LSM > BP after 1–2 weeks	Evaluation, treatment, referral
Step II	Check 4-limb BP LSM > BP after 6 mo	Check 4-limb BP LSM > BP after 1–2 weeks	
Step III	ABPM Evaluation	ABPM Evaluation, treatment	

LSM: Life style modifications, ABPM: Ambulatory BP monitoring
*After excluding secondary causes

and nephropathy. Whether children with essential hypertension continue to have hypertension in adulthood, is uncertain.

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CHAPTER

18

Disorders of Central Nervous System

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Neurological disorders account for ~15–20% of hospitalizations, which may be divided into three major categories: (a) central nervous system disorders, involving brain and spinal cord, (b) neuromuscular disorders involving peripheral nerves and muscles, and (c) rare disorders of autonomic nervous system.

18.1 CLINICAL EVALUATION IN NEUROLOGICAL DISEASE

Primary aim of clinical evaluation in a suspected neurological disease is to: (a) localize the site of lesion (topographic diagnosis) and (b) identify the probable cause of lesion (etiological diagnosis), based on detailed history, general examination and neurological examination.

History: Possibility of a neurological disease should be considered in presence of one or more of following complaints: (a) altered sensorium or behavioral changes, (b) seizure or movement disorders, (c) motor deficits, (d) abnormal vision, hearing or speech, (e) sensory or autonomic disturbances, (f) developmental delay/regression or mental retardation.

Each of these complaints should be assessed for—*onset* (sudden/insidious), *progression* (static, progressive or improving) and *duration* (short, long, since birth). Other important histories in neurological disease include: (a) family history of neurological or behavioral illness, (b) perinatal history of complications, (c) history of head/spinal trauma, (d) thorough developmental history.

General examination should be specifically directed towards: (a) *anthropometry*, e.g. head circumference for microcephaly/hydrocephalus; (b) *vital signs*, e.g. BP, HR, RR, which are frequently abnormal in presence of raised intracranial pressure or autonomic disorders; (c) *cutaneous stigmata* for neurocutaneous disorders; (d) *dysmorphic features* in congenital anomalies; (e) extracranial *septic/tubercular foci;* and (f) *spinal tenderness*/deformities.

Neurological examination of a child requires considerable patience and flexibility; and includes five major areas of assessment: *(a) higher functions, (b) signs of meningeal irritation, (c) cranial nerves, (c) motor system, (d) sensory system, (e) localizing signs including soft neurological signs.*

A. Assessment of higher functions, unlike adults, is usually based on simple observations rather than specific tests, with useful inputs from parents and includes assessment of: (a) *general behavior*, e.g. irritability, drowsiness, confusion, (b) *general intellect, comprehension and memory,* (c) *orientation* to time, space and person, (d) adequacy/fluency of *Speech.*

Sensorium should be recorded in terms of *Modified Glasgow coma scale*, if possible, which also helps to monitor changes over time (*see* **Table 18.7)**.

However, it is often difficult to assess a young child in isolated fields of higher functions and all cases should at least be categorized as: (a) conscious, (b) comatose, or (c) delirious (Ch 18.3). *Vegetative state* is a term commonly used to refer the patients "*in a wakeful state and not unconscious, but are not aware of the surroundings*".

B. Signs of meningeal irritation are produced due to inflammation of spinal meninges, leading to irritation of nerve roots and protective spasm of spinal muscles on stretching of spinal cord. Important signs of meningeal irritation include:

- *Nuchal rigidity*, i.e. pain and stiffness of neck, during its flexion.
- *Kernig sign*, i.e. pain on extension of the leg, following hip flexion.
- *Brudzinski sign*, i.e. involuntary flexion of knee and hips, on passive flexion of the neck.

C. Examination of cranial nerves: While formal cranial nerve examination is possible only in older children, all except olfactory nerve may be assessed even in infants or comatose children with age-appropriate methods, as follows:

- ***Olfactory nerve*** evaluation is often difficult, unreliable and unnecessary. *Anosmia* in children is usually transient, due to local rhinitis.

- ***Optic nerve*** in infants and toddlers is best assessed by fundus examination, though older cooperative children may be assessed for—*(a) visual acuity, (b) field of vision* and *(c) color vision.*

  In young/comatose children, *menace reflex* (reflex blinking to a sudden menacing ot threatening gesture towards patient's eye) or *light reflex* may be used as an indicator of optic nerve function, other causes, e.g. opaque media (cataract) are excluded.

  Field of vision may be informally tested by observing the movements of eyes, following a colourful moving object.
- ***Extra-ocular nerves*** (occulomotor, trochlear and abducens) are tested by range of extraocular movements in different directions, which may require *Doll's eye maneuver i*n young/comatose children.

  Doll's eye maneuver involves observation of eye movements after sudden turning of head on one side, which leads to conjugate deviation of eyes on other side. Absence of this oculocephalic response indicates external ophthalmoplegia on opposite side of head movement. Maneuver needs to be repeated on other side as well as after flexion and extension of neck.

  Occulomotor palsy is also characterised by—(a) ptosis and (b) loss of accommodation.

  Lateral gaze palsy due to abducens involvement, is usually a false localizing sign in raised intracranial pressure due to longest intracranial course of nerve.

  Presence of vertical, rotatory or horizontal *nystagmus* indicates vestibular, cerebellar or brain stem disease, while skew deviation of eyes indicates cerebellar or pontine lesion.
- ***Trigeminal nerve*** is a mixed nerve with three divisions-ophthalmic, maxillary and mandibular. Sensory functions are tested by *corneal reflex* and *facial sensations*, while motor functions are assessed by mastication activity and *jaw jerk*.
- ***Facial nerve*** innervates muscles of facial expression (motor) and anterior 2/3rd of tongue (taste). Important signs of facial palsy include—(i) asymmetric facial expressions, (ii) lesser nasolabial fold on affected side on cry, smile, teeth-clenching etc., (iii) asymmetric palpebral fissure with inability to close the eye on affected side, (iv) drooling of saliva and feeds from weaker side.

  Absence of creases on forehead while child is frowning or looking upwards, indicates *infranuclear facial palsy (d/d supranuclear palsy),* as upper face receives cortical innervation from both sides.
- ***Vestibulo-cochlear nerve*** involvement should be suspected in cases with deafness, tinnitus or vertigo. *Vestibular* component is difficult to assess in young children, unless vertigo is complained.

  Auditory component may be tested by standard *Rinni's* or *Weber's* test in older children, while young children may be assessed by response to familiar sounds or *startle response.* Audiometry is a part of routine assessment in high-risk children.
- ***Glossopharyngeal, vagus and accessory nerve*** lesions often co-exist due to proximity of their nuclei in brainstem and common cranial outlet via jugular foramen. Supranuclear or *pseudobulbar palsy* of these nerves is less common than infranuclear *bulbar palsy*.

  Important signs of bulbar or pseudobulbar palsy include—(a) absence of gag reflex, (b) asymmetry of soft palate with uvular deviation, (c) hoarseness of voice or nasal twang, (d) difficulty in swallowing, and (e) nasal regurgitation of feeds. Winging of scapula and inability to shrug the shoulders indicates XI nerve paralysis.
- ***Hypoglossal nerve*** is a purely motor nerve of the tongue and assessed by observing shape, asymmetry (unilateral lesion), and fasciculations of tongue. Inability to protrude the tongue indicates bilateral XII nerve palsy.

D. Examination of motor system should be preceded by assessment of musculoskeletal system, especially for painful inflammatory disorders, to avoid misinterpretation of neurological findings. Important steps in motor evaluation include examination of—*(a) gait, (b) posture, (c) muscle bulk, (d) tone, (e) power, (f) reflexes, and (g) coordination.*

a. ***Gait:*** Abnormal but *painless* gait is an indicator of neuromuscular disease **(Table 18.1)**, which should be differentiated by developmental or painful gait of orthopedic disorders (Ch 23.3).

b. ***Posture:*** Common postural abnormalities in CNS disorders are as follows:
   - *Decorticate posture* (bilateral flexion of upper limbs and extension of lower limbs) in pyramidal tract lesion above/at the level of internal capsule.

TABLE 18.1: Common gait abnormalities

- **Spastic or hemiplegic** (Cicumduction of legs)\
  In pyramidal tract lesion
- **Scissoring** (Crossed leg walking)
  In cerebral palsy
- **High-stepping** (Excess lifting of affected foot)
  In peripheral neuropathies or contractures
- **Stamping** (High-stepping > forceful grounding)
  In post. column lesions (loss of position sense)
- **Ataxic** (Staggering with side-swaying)
  In cerebellar or extrapyramidal lesion
- **Shuffling** (Forward swaying, with rapid steps)
  In extrapyramidal lesions (rare in children)
- **Waddling gait** (Side to side swaying of hips)
  In hip-girdle weakness, e.g. DDH, DMD
- **Antalgic gait** (Painful)
  In inflammatory or orthopedic leg problems

DDH: Developmental dislocation of hip; **DMD:** Duchhene muscular dystrophy.

- *Decerebrate posture* (extension of all limbs, with spasticity) in mixed pyramidal and extrapyramidal lesions, usually at brainstem level (*see* **Fig. 18.11)**
- *Frog-like posture* (extension of all four limbs with hypotonia) in generalized neuromuscular disorder (floppy child), though painful conditions, e.g. scurvy, should be excluded.
- *Asymmetric posture* indicates focal motor lesions, nerve injuries (foot/hand-drop) or contractures.
- *Ill-sustained posture* indicate sensory or cerebellar ataxia. A positive *Romberg sign*, i.e. inability to maintain steady posture on standing with open eyes, indicates cerebellar ataxia. In sensory ataxia, Romberg sign is positive with closed eyes but negative with open eyes.

c. ***Bulk*** of different muscles is assessed by observation and comparing from other side. In doubtful cases, recording of limb circumference on both sides is required to detect unilateral wasting (neuropathies) or pseudohypertrophy (myopathies). Muscle bulk is normal upper motor neuron lesions, except in later stages due to disuse atrophy.

d. ***Muscle tone*** must be assessed for *passive tone* by-(a) abnormal posture, (b) soft/flabby or stiff feel, or *active tone* by (c) shaking the unsupported limb for range and frailty of movements, and (d) degree of resistance on passive joint movement. It should always be compared from other side.

Common tone abnormalities include: (a) *clasp-knife spasticity* (initial resistance to movement) in pyramidal tract lesions, (b) *cog-wheel rigidity* (jerky, intermittent resistance) or *lead-pipe rigidity* (uniform resistance) in extrapyramidal lesions, (c) *hypotonia* in cerebellar or neuromuscular disorders.

Vertical suspension of a young infant, holding from axilla, is a useful method to assess the tone. *Scissoring* of lower limbs or arching of back in this position indicates hypertonia (cerebral palsy), while hypotonic floppy child tends to slip from axillary grip.

e. ***Muscle power*** must be assessed and graded **(Table 18.2)** in different group of muscles at different joints, by passive observation of spontaneous movements and active testing of strength against gravity/resistance. Examination of power also includes testing for *Gower sign* (Ch 18.16.4) and muscles of respiration (*paradoxical respiration).*

f. ***Reflexes:*** Examination of reflexes includes assessment of superficial, deep and neonatal reflexes (in newborns and suspected cerebral palsy) as well planter response. Asymmetry of reflexes has important localizing value.
- Important *superficial reflexes* include conjunctival or corneal reflex (V/VII cranial nerve), abdominal reflex ($T_{8–12}$), cremasteric reflex (L_1), and anal reflex ($S_{3–4}$). Superficial reflexes are lost in lower motor neuron lesions.
- Important *deep tendon reflexes* with their root palsy include jaw jerk (pontine reflex), biceps (C_5), triceps ($C_{6–7}$), supinator (C_6), knee ($L_{3–4}$), and ankle (L_5-S_1). Deep tendon reflexes must be graded according to the strength of response **(Table 18.3)**. Presence of patellar and ankle clonus is an unequivocal sign of pyramidal tract lesions.

Abnormal deep tendon reflexes include: (a) hyperreflexia in upper motor neuron lesions, (b) hypo-/a-reflexia in lower motor neuron lesions and (c) pendular jerks in cerebellar disorders.

g. ***Plantar response*** is assessed by *standard method* (stroking on lateral border of sole), though other techniques may be useful in cases with equivocal response, e.g. *Oppenheim's maneuver* (pressure on tibial shin), *Gordon's method* (squeezing of tendo Achillis) or *Chaddock's sign* (scratching on lateral malleolus).

Extensor planter response (positive *Babinski sign*) has two components—(i) extension of great toe and (ii) fanning of other toes, and indicates upper motor neuron lesion. However it may be physiological in infancy due to incomplete myelination or during sleep. Fanning of the toes is usually absent in physiological extensor planter response.

h. ***Neonatal reflexes*** and their significance is discussed in Chapter 12.5. While asymmetric neonatal reflexes, e.g. Moro's reflex indicate local pathology, persistence of neonatal reflexes beyond normal timing of their disappearance is seen in cerebral palsy.

i. ***Coordination*** is tested by *finger-to-nose test* in upper limbs and *heel-to-shin test* or *tandem walking* in lower limbs. Abnormal coordination signifies cerebellar or sensory dysfunction. Inability to perform these tests

TABLE 18.2: Grading of muscle power (MRC*)

Grade	*Response*
0	No movements
I	Flickering movements
II	Active movements, but not against the gravity
III	Movements against the gravity
IV	Movements against active resistance
V	Normal power

MRC: Medical Research Council

TABLE 18.3: Grading of deep Tendon reflexes

Grade	*Response*
0	Absent (Areflexia)
I+	Weak (Hyporeflexia)
II+	Normal*
III+	Brisk (Hyperreflexia)
IV+	Presence of clonus

*Knee jerk may be normally brisk. Pathologically brisk knee jerk is often accompanied by crossed adductor response, i.e. contraction of contralateral adductors

even with open eyes indicate cerebellar lesion. Other methods to assess co-ordination include gait, hand-writing, dysdiadochokinesia, etc.

E. Sensory examination is difficult in pre-school children (except for pain), while older and cooperative children, specially those with spinal disorders, should be tested for—(a) *pain* by pin-prick, (b) *light touch* by cotton-wool, (c) *deep touch* by finger-pressure, (d) *temperature* by hot/cold water test-tubes, (e) *position* sense by great toe manipulation, and (f) *vibration* sense by tuning-fork, to localize the spinal level of disease.

Other cortical senses, e.g. *two-point discrimination* (using a protector with two legs 1 cm apart), *sensory inattention* (missing one of the sensations, when two points are stimulated together) and *astereognosis* (inability to identify an object by touch, without visualization) may be assessed in cooperative children.

F. Abnormal movements, e.g. chorea, athetosis and tremors are easily noticeable on simple observation (Ch 18.9). Specific clinical signs for chorea include milk-maid grip, lizard-tongue, etc. (Ch 17.6). Tremors are best tested on outstretched fingers in a co-operative child. Presence of these movements indicates extra-pyramidal pathology.

G. Urinary bladder dysfunction is an important diagnostic clue in spinal disorders. Bladder function is regulated by three neural mechanisms—(a) excitatory parasympathetic flow (S_{2-3}), inhibitory sympathetic flow (L_{1-2}) and voluntary corticospinal flow. Common types of bladder involvement in CNS disease are:

- *Reflex or automatic* bladder, i.e. urinary retention with intermittent reflex emptying in upper motor neuron lesions above the lumbar region, due to cut-off of voluntary control but preserved reflex arc.
- *Persistent urinary incontinence* in lumbar or cauda equina lesions due to cut-off of inhibitory sympathetic flow.
- *Autonomic bladder,* i.e. persistent urinary retention with overflow incontinence in peripheral nerve injury due to loss of excitatory parasympathetic flow.

In addition, upper motor neuron spinal lesions are also associated with constipation, while peripheral nerve injury may lead to fecal incontinence.

Clinical Localization of Lesion

For the sake of broad anatomical localization, neurological findings may divided into:

A. Cerebral cortex (gray-matter) lesions are characterized by: (a) higher function abnormalities, (b) seizures, (c) speech/vision defects and (d) soft neurological signs, etc. Signs of specific cortical lobe involvement are given in **Table 18.4**.

TABLE 18.4: Localizing signs of cortical lesions

Frontal lobe	***Temporal lobe***
Altered behavior/sensorium	Learning disabilities
Seizures	Impaired memory
Aphasia*	Dysphasia
Loss of cortical sensations	Auditoryloss/hallucinations
UMN signs	Psychomotor seizures
Parietal lobe	***Occipital lobe***
Learning disabilities	Homonymous hemianopia
Homonymous hemianopia	Visual agnosia
UMN signs	Visual hallucinations

*In lesions of dominant hemisphere

TABLE 18.5: D/D UMN *vs* LMN lesions

Signs	***UMN***	***LMN***
Muscle bulk	Normal	Wasting
Tone	Increased	Reduced
Superficial reflexes	Present	Absent
Tendon reflexes	↑↑	↓↓/Absent
Plantar response	Extensor*	Flexor
Muscle fasciculations	Absent	Present

*Positive *Babinski sign*

B. Motor neuron (white-matter) dysfunction are broadly divided into upper (UMN) and lower (LMN) motor neuron lesions **(Table 18.5)**. Motor deficits may range from minor functional defects to well-defined clinical presentations, e.g. *Hemiplegia*, i.e. unilateral weakness, *Paraplegia*, i.e. weakness of both lower limbs, *Quadriplegia*, i.e. weakness of all four limbs, *Diplegia*, i.e. spastic weakness of all four limbs but more prominent in lower limbs, and *Monoplegia*, i.e. weakness of only one limb. Hemiplegia is almost always a UMN lesion (Ch 18.7), while paraplegia may be of either UMN or LMN etiology (Ch 18.16). Quadriplegia/diplegia is mainly seen cerebral palsy, except a few cases of high cervical spine lesions. Monoplegia usually indicates peripheral nerve injury or mild cerebral palsy.

C. Cerebellar dysfunction presents with:

- Ataxic gait/posture (*Romberg* sign)
- Generalized hypotonia
- Hyporeflexia or pendular jerks
- Ocular signs-nystagmus, skew deviation
- Dysarthria
- Impaired coordination, e.g. *dysmetria* (finger nose test) or *Dysdiadochokinesia* (alternate pronation/supination)

D. Extrapyramidal dysfunction presents with:

- Abnormal movements, e.g. chorea or athetosis
- Dystonia
- Decerebrate posture
- Speech impairment

- Vacant, expressionless face (rare in children)
- Shuffling gait (rare in children)

Etiological Categorization of Lesions

According to pathological type of lesion, neurological disorders may be: (a) infective or inflammatory, (b) vascular, (c) neoplastic, (d) degenerative, or (e) traumatic, in origin, apart from congenital anomalies.

- **Infective or inflammatory lesions** are commonest cause of neurological disease in younger children, presenting with fairly acute onset (of a few days) and progress rapidly unless treated. Presence of fever, extracranial septic foci or toxaemia strongly indicates infective pathology.
- **Vascular lesions** are typically acute catastrophic in onset, developing over few minutes and recovery starts within few days. Fever may be present or absent, depending on the etiology. BP must always be examined in these cases.
- **Neoplastic or other space occupying lesions**, e.g. tuberculoma, neurocysticercosis or hematomas are slowly progressive, with gradual onset over a few weeks. Raised intracranial pressure *or* seizures are predominant presentation in infratentorial and supratentorial space occupying lesions, respectively.
- **Traumatic lesions** present either immediately after head injury with acute signs of cerebral or motor dysfunction and/or raised intracranial pressure *or* after many weeks as space-occupying lesions due to formation of subdural hematoma.
- **Degenerative lesions**, rarest of neurological disorders, present with long history of indeterminate onset, often as waxing and waning course. Regression of milestones is usually the first complaint in young children, while older cases may present with behavioral changes, poor school performance, seizures or UMN signs. Family history is common.
- **Congenital anomalies** usually manifest at birth as obvious *structural defects*, e.g. microcephaly/hydrocephalus, meningomyelocele, etc.; or detected in early infancy during evaluation for *functional defects*, e.g. developmental delay, spasticity/flaccidity, seizures, etc.

18.2 LABORATORY EVALUATION IN CNS DISEASE

Important investigations in neurological disease include: (a) CSF examination, (b) neuroimaging, (c) electrophysiological studies and (d) others, e.g. nerve or muscle biopsy, enzyme studies, etc.

CSF examination, from the fluid obtained via *Lumbar puncture* is the baseline investigation in most neurological disorders, specially *indicated* for:

- Diagnosis of meningitis, encephalitis, subarachnoid hemorrhage, etc.
- Assessment of CNS involvement in septicemia, leukemia, etc.
- D/D between poliomyelitis and Guillain-Barré syndrome
- CSF sample collection for antibody testing, metabolic disorders, etc.
- Therapeutic reduction in raised ICP.

Lumbar puncture (LP) is *contraindicated* in cases with: (a) papilledema, (b) anatomical defect or local infection at the puncture site, (c) thrombocytopenia <20,000/mm^3, (d) midline-shift in CT brain, and (e) hemodynamic instability. *Fundus exam for papilledema is essential before LP* to exclude raised ICP, as sudden release of pressure may result in medullary coning and cardiorespiratory arrest.

Complications are rare after LP but some cases may develop—(a) sudden death due to coning of brain stem, (b) iatrogenic meningitis (exogenous infection), and (c) local inclusion dermoid after many years. For procedural details of LP, *see* Ch 32.6.

Important CSF findings in normal children as well as common CNS infections **(Table 18.6)** include:

- *Pressure* (N: 80–100 mmH_2O) may be elevated in intracranial infections, tumors and crying child; while low pressure or dry tap indicates spinal block in extramedullary spinal tumors or due to thick pus in bacterial meningitis.
- *Color:* CSF is colorless, except in newborns who may have xanthochromic CSF due to high protein and bilirubin content. Common color abnormalities include: *Xanthochromic* in Froin syndrome or old sub-

TABLE 18.6: CSF findings in normal child and in common CNS infections

	*Normal**	*Pyogenic meningitis*	*Tubercular meningitis*	*Encephalitis*
Pressure (mm/fluid)	80–100	Elevated	Elevated	↑N/Elevated
Color	Watery	Turbid	Straw-color	Clear
Proteins (mg/dl)	10–40	↑↑↑(> 200)	↑↑(> 100)	N/↑ (20–100)
Sugar (CSF/blood ratio)	40–60 (~66%)	↓↓↓/absent	↓(< 50%)	N
Cells (cells/mm^3)	< 5	↑↑↑(> 200)	↓↓(50–100)	N/↑
Predominant cells	Lymphocytes	Polymorph	Lymphocytes	Lymphocytes
Organisms	Sterile	Present	AFB ±	Viral tests

arachnoid bleed, *Cloudy* in pyogenic meningitis, *straw-colored* in tubercular meningitis and *Red* in traumatic or subarachnoid hemorrhage.

Differentiation between traumatic and hemorrhagic CSF is difficult, though progressive clearance of color during CSF collection in 2–3 different test tubes indicates traumatic LP.

- *Cobweb* formation after 2–3 hours (due to high fibrinogen content) indicates TBM.
- *Elevated proteins* (N: <40 mg/dl) indicate meningitis, though mild elevation (<100 mg/dl) is common in newborns, encephalitis, traumatic LP, subarachnoid bleeds, degenerative disorders and Guillain-Barre syndrome.
- *Elevated cell count* (N: <5 cells/mm^3) indicates meningitis, though mild pleocytosis (<50 cell/mm^3) may be seen in newborns, poliomyelitis, brain tumors, demyelinating diseases, etc. Presence of even a *single* polymorph in non-traumatic CSF indicates bacterial meningitis, except in newborns.
- *Hypoglycorrhachia* (↓glucose) indicate bacterial consumption of glucose in meningitis. Normal CSF glucose is about 2/3rd of blood levels.
- *Bacteriological examination* of CSF is indicated in all cases for gram staining, bacterial cultures and AFB staining/culture. Fungal cultures as well as viral studies, e.g. PCR are indicated in select cases.
- Selected samples may also be tested for antibodies (autoimmune encephalitis, SSPE) or metabolites, e.g. lactates (metabolic disorders).

Neuroimaging studies include plain skull skiagrams, cranial ultrasound, CT scan, MRI, brain scan with contrast and vascular studies, e.g. angiography or venogram.

Plain skull X-ray is rarely useful in neurodiagnosis, except in suspected skull fractures, chronic raised intracranial pressure (ICP) and calcifications. X-ray skull should be specially looked for:

- Sutural separation (↑ICP) or thickening/premature fusion (craniosynostosis).
- Diploe space narrowing (↑ICP) or widening (hemolytic anemia).
- Copper/silver beaten appearance (↑ICP) due to impressions of enhanced cortical sulci-gyri, pressing over inner table of skull **(Fig. 18.1)**.
- Visible skull fractures.
- Calcifications (Intrauterine infections, Sturge-Weber syndrome).
- Eroded anterior clinoid process (craniopharyngioma).
- Mastoid sclerosis (chronic ear disease).

Cranial ultrasound is useful in newborns and infants with open fontanelle to assess central structures, e.g. ventricles and paraventricular region but peripheral cortex, subdural spaces and posterior fossa is not well visualized on USG.

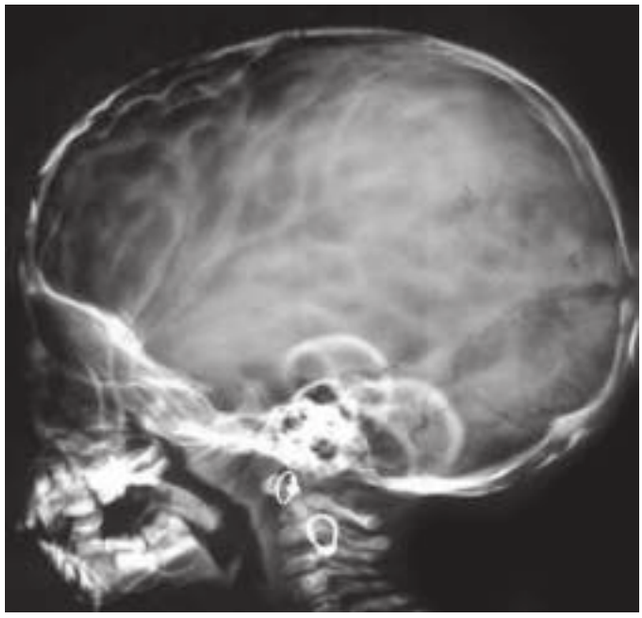

Fig. 18.1: X-ray skull: Silver-Beaten appearance in raised intracranial pressure.

Computerized tomography (CT) provides comparable information to MRI in intracranial structural lesions, which may be broadly classified as *hypodense*, *isodense* and *hyperdense*. Hypodense lesions are produced by presence of fluid, e.g. in edema, necrosis, infarcts, hydrocephalus, cysts etc while hyperdense lesions are seen in hemorrhage, calcifications, tumors, etc.

CT scan is preferred over MRI to visualize skull fractures and calcifications, while posterior fossa lesions and myelination disorders may be missed on CT. Radiation exposure is another risk with CT scan.

Contrast CT is useful in cases with altered vascularity, i.e. infarcts, cerebral edema, hemorrhage, tumors or abscesses.

CT angiography is often used to visualize cervical and intracranial vascular structures as high density lesions, specially in older children.

Magnetic resonance imaging (MRI) is generally preferred over CT scan for neuroimaging due to the advantage of structural as well as functional assessment without exposure to radiation. However, it is relatively costly and may need anesthesia in younger children.

MRI is preferred investigation in—(a) degenerative/demyelinating disorders, (b) cerebral edema, (c) posterior fossa lesions, (d) spinal cord lesions, and (e) before neurosurgery. However, calcifications are not well visualized on MRI.

Different imaging sequences in MRI include **T1** images for structural lesions, $\mathbf{T_2}$ images mainly for function lesions and **flair** (Fluid attenuation inversion

recovery) images to detect CSF signals in peripheral and periventricular lesions. Diffusion weighted images (DWI) are useful to assess water movements, e.g. in cytotoxic edema.

MR-angiography or venography is the investigation of choice in suspected intracranial vascular malformations and strokes.

Functional MRI is a non-invasive technique to map neuronal activity based on cerebral blood flow and oxygenation, useful for pre-surgical localization of critical brain functions, e.g. before epilepsy surgery.

MR spectroscopy is a molecular imaging technique to assess neurochemical profile of a selected brain region, e.g. presence of N-acetylaspartate, creatine, lactate, etc. This information is useful in diagnosis of inborn errors of metabolism, cortical dysplasia, and hypoxic-ischemic injury. It also helps to differentiate tuberculoma (*lipid peaks*) from neurocysticercosis (*amino acid peaks*) and in pre-operative or post-therapeutic assessment of intracranial tumors.

Radionuclide brain scan with ^{99}Tc, positron emission tomography (PET) or single photon emission computerized tomography (SPECT) helps to study regional blood flow and integrity of blood-brain barrier. Brain scans are specially useful in herpes encephalitis, autoimmune encephalitis, cerebrovascular disease and to localize small epileptic foci.

Cerebral angiography *(with digital substraction)* is useful for evaluation of vascular disorders of brain, though MR-angiography has reduced the need of more invasive angiographies in recent years.

Electrophysiological studies are useful to assess the functional status of neurons even in absence of structural abnormalities, specially in epilepsy and peripheral neuromuscular disorders, as follows:

Electroencephalography (EEG) is a continuous recording of electrical activity between two reference scalp electrodes, to study rate, amplitude, symmetry and morphology of electric rhythms.

Normal EEG waves are classified according to frequency as-delta (1–3/sec), theta (4–7/sec), alpha (8–12/sec) and beta (13–20/sec) waves. These waves are altered by many factors, e.g. age, sleep, diseases, drugs, etc. Normal background rhythm in newborn is low amplitude, low frequency (delta/theta waves) that gradually changes to alpha rhythm by 5–7 years.

Uses: EEG is mainly useful to—(a) differentiate seizure from non-seizure disorders, (b) diagnose specific epileptic syndromes, (c) diagnose some degenerative (SSPE), infective (herpes encephalitis) or metabolic (pyridoxine dependency) disorders, and (d) decide about anticonvulsant therapy.

Important EEG abnormalities may be generalized, localized or lateralized, including either presence of epileptiform discharge (paroxysmal, sharp waves or spikes, high voltage) or abnormal slowing of rhythm. Important diagnostic abnormalities are seen in:

- *Absence seizures:* 3 per second spike and wave form.
- *Infantile spasms:* Hypsarrhythmia (high voltage, slow wave pattern) with superimposed spikes.
- *SSPE:* Repeated bursts of high-voltage, slow-wave complexes.
- *Rolandic epilepsy:* Repeated high amplitude spikes, originating from rolandic area.
- *Herpes encephalitis:* Periodic lateralized epileptiform discharges from centrotemporal regions
- *Focal epileptiform discharges or slowing* are seen in structural lesions, e.g. malformations, infarcts, tumors and other space occupying lesions.
- *Diffuse background slowing* usually indicates diffuse neuronal injury, e.g. in toxic or metabolic encephalopathies.

Caution: EEGs may be abnormal in ~2% of normal population and should be interpreted cautiously with clinical correlation. On the other hand, EEG may be occasionally normal during interictal phase in epilepsy.

EEG abnormalities may be precipitated by provocation procedures, e.g. sleep deprivation or photic stimulation. Polygraphic or video-EEG recordings for long periods are recent innovations in detection of subtle seizures and epileptic foci.

Electromyography (EMG) is mainly used to distinguish myopathies from neuropathies, though specific diagnosis of myopathic disorder is rarely possible on EMG.

Nerve conduction studies (NCS) is an age-dependent parameter, indicated in diagnosis of neuropathies and subclinical involvement in systemic disorders, based on parameters like amplitude, nerve conduction velocity (NCV) and latency. Decreased NCV is indicative of myelin injury whereas reduced amplitude indicates axonal injury.

Other electrophysiological studies, e.g. visual evoked potentials (VEP), brain stem auditory evoked potential (BAEP) and somatosensory evoked potentials (SSEP) are specially useful in young, uncooperative and comatose children for early diagnosis of neurological insults in high-risk cases.

18.3 COMATOSE CHILD

Coma is a clinical state of varied etiology, characterized by *altered consciousness, from which the child cannot be aroused by ordinary verbal or physical stimuli.*

Pathophysiology: Maintenance of consciousness, i.e. awareness about self and environment, is the function of *Reticular activating system*, a network of neurons in upper brain-stem with inputs from other parts of brain, especially cerebral cortex.

TABLE 18.7: Modified *Glasgow* coma scale

*Score**	*Eye opening*	*Best motor response*	*Best verbal response*
6	–	Obeys command	–
5	–	Localize pain	Well oriented
4	Spontaneous	Flexion withdrawal	Confused conversation
3	To verbal stimuli	Decorticate posturing	Inappropriate words/persistent cry
2	To pain	Decerebrate posturing	Incomprehensible sounds, grunts
1	No response	No response	No vocal response

*Combined score of < 7 suggests definite coma. (also *see* text)

While many terms are used for altered states of consciousness, it may be broadly classified as:

- *States of depressed consciousness*, e.g. obtundation, stupor or coma of variable severity.
- *States of hyperexcitability*, e.g. agitation, confusion, delusions, hallucinations or delirium.
- *Vegetative state*, i.e. a wakeful state with preserved sleep-wake cycle but without any awareness about surroundings.

Clinically, presence and severity of coma is usually best assessed on ***Modified Glasgow coma scale or GCS* (Table 18.7)**, using three variables, i.e. Eye opening ($E_{1–4}$), motor response to painful stimuli ($M_{1–6}$) and response to verbal commands ($V_{1–5}$). A GCS score of <7 indicates *definite coma*, though most cases with score of 7 or 8 are also comatose. GCS score may also be described in terms of individual variables, e.g. as $E_4M_5V_3$.

In routine clinical practice, depth of coma may also be simply graded as:

- *Grade I (stupor):* Momentarily arousable on verbal/physical stimuli,
- *Grade II (light coma):* Not arousable, but moans on painful stimuli with limb withdrawal,
- *Grade III (deep coma):* No response to painful stimuli with decorticate/decerebrate posture,
- *Grade IV (brain death):* No pupillary reaction and spontaneous breathing, though spinal reflexes may be present.

Persistence of grade IV coma for more than 4 hours, may be considered as an indicator of irreversible brain damage.

Etiology of coma may be broadly divided into four groups: (a) Infections, (b) Hypoxia/Ischemia, (c) Metabolic/Toxic disorders, and (d) Traumatic head injury **(Table 18.8)**. It is also a terminal event in vascular or degenerative neurological disorders as well as a sign of severely raised intracranial pressure (ICP).

Diagnostic evaluation in comatose patients may be delayed till initial resuscitation restoring patent airways, adequate breathing and circulation, and includes:

A. Detailed history, specially related to:

- Onset and progress of coma
  - *Sudden:* Vascular, toxic or traumatic etiology
  - *Gradual:* ICSOL or degenerative lesions
- Preceding illness, e.g. diabetes, epilepsy, etc.
- Head injury, accidents and poisoning
- Fever (infective, heat stroke)
- Family history of epilepsy or psychiatric problems.

B. General examination:

- *Temperature*
  - *Hypothermia:* Poisonings, shock, etc.
  - *Fever:* Infection, subarachnoid hemorrhage, etc.
  - *Hyperthermia:* Heat stroke, pontine lesions.
- *Heart rate*
  - *Bradycardia:* Raised ICP, narcotic poisonings.
  - *Tachycardia:* Shock, atropine poisoning.
- *Blood pressure*
  - *Hypertension:* Raised ICP, encephalopathy.
  - *Hypotension:* Shock, poisonings.

TABLE 18.8: Causes of coma in childhood

- **Infective**
  Local—meningitis, encephalitis, brain abscess
  Systemic—cerebral malaria, septicemia, typhoid
- **Metabolic**
  Hypoglycemia, diabetic ketoacidosis
  Hepatic encephalopathy, Reye syndrome
  Uremia — acute or end-stage renal failure
  Severe dehydration or water intoxication
  Dyselectrolytemia — hyper/hyponatremia, acidosis
- **Toxic**
  Poisonings - barbiturates, narcotics, and others
  Snake bite, scorpion sting
- **Traumatic**: Head injury
- **Hypoxic**
  Acute respiratory failure
  Accidents: CO poisoning, near-drowning
- **Vascular**
  Shock/syncope
  Hypertensive encephalopathy
  Cerbrovascular strokes
  Cerebral edema (raised ICP)
- **Others**
  Status epilepticus (post-ictal)
  Heat stroke, severe hypothermia
  Hysteria (conversion reaction)

- *Respiration*
  - *Cheyne-Stokes breathing:* Bilateral cortical damage.
  - *Irregular and deep:* Brainstem lesions.
  - *Irregular and shallow:* Narcotic poisoning.
  - *Acidotic:* Diabetic ketoacidosis, salicylism, etc.
  - *Breath odor: Fruity* in diabetic ketoacidosis, *Fetor hepaticus* in liver disease, *foul* in uremia.
- *Pupils*
  - *Bilateral fix and dilated:* Atropine poisoning, terminal.
  - *Unilateral fix and dilated:* Tentorial herniation.
  - *Fixed in mid-position:* Mid-brain lesions.
  - *Pin-point:* Morphine poisoning, pontine lesion.
- *Eye movements*
  - *Spontaneous movements:* Conjugate deviation in cortical lesion, contralateral in irritation of gaze centers, ipsilateral in complete injury.
  - *Oculocephalic (Doll's eye) response:* Absent in brainstem lesion, preserved in cortical lesions.
  - Oculovestibular response, i.e. ipsilateral deviation of eyes on cold-water irrigation of auditory canal is absent in brainstem lesion.
  - Absent oculocephalic and oculovestibular response but preserved light reflex is a hallmark of metabolic encephalopathy.
  - *Nystagmus:* Cerebellar or posterior fossa lesion.
- *Skin/mucosal findings:*
  - ↓ sweating/salivation in atropine poisoning
  - ↑ sweating/salivation in organophosphorus poisoning
  - Icterus in hepatic failure
  - Purpuric spots signs of intracranial hemorrhage
  - Abnormal smells in poisonings
  - External injury marks in traumatic coma

C. Neurological examination:

- *Abnormal posture*
  - Decorticate (cortical)
  - Decerebrate (brain-stem lesion)
- *Neck rigidity* in meningitis, subarachnoid bleed.
- *Localizing motor signs* in ICSOL, strokes.
- *Signs of raised ICP* in infections, metabolic, ICSOL, etc.
- *Abnormal movements,* e.g. Athetosis/myoclonus in hypoxic/metabolic coma. Seizures are of little diagnostic value.
- *Fundus* examination is essential in all cases to detect papilledema, and retinal hemorrhages.

D. Laboratory investigations, depend on suspected cause and include:

- *CSF examination*
- *Biochemical studies*, e.g.
  - Blood sugar
  - Serum electrolytes sp. Na^+, Ca^{++} and HCO_3
  - Liver function tests including serum ammonia
  - Renal function tests, e.g. BUN, serum creatinine
  - Arterial blood gases
  - Metabolic screening for inborn errors
- *Hematological studies*
  - Peripheral smear for malaria
  - Platelet count and clotting profile for IC bleeding
- *Urinalysis*
  - Benedict test for diabetic ketoacidosis
  - Ferric chloride test in selected cases
  - Purple color in ketosis or salicylate poisoning
  - Green color in phenothiazine or INH poisoning
- Gastric aspirate for toxic screen in poisoning
- *Neuroimaging* with CT/MRI
- *EEG* for HSV encephalitis, seizure disorder
- *Microbial cultures from* CSF/blood/other sites
- *Serology*, e.g. antibody titers for viral or autoimmune encephalitis

Management: Coma is a medical emergency and all cases need intensive care. Important components of care include—(a) Restoration of vital functions, (b) General nursing care, (c) Continuous monitoring, (d) Treatment of complications, e.g. seizures and raised ICT, and (e) Treatment of primary cause.

a. Immediate resuscitation (ABC):

- ***A***irway patency needs to be ensured with repeated suction and oral airway.
- ***B***reathing support with oxygen and ventilator assistance, if needed.
- ***C***irculatory support with fluids and inotropic agents, e.g. dopamine, if needed.

b. General nursing care:

- *Nursing position,* preferably in lateral head-down (recovery) position to facilitate draining of secretions and prevent aspiration.
- *Nutrition* via IV route in initial stages. Nasogastric feeds may be given in stable, prolonged coma.
- *Care of back* with frequent change of posture, keeping the under-bed dry and application of fine dusting powder on back, to prevent bed-sores.
- *Care of bladder* with regular emptying of bladder by manual compression/hot fomentation to prevent urinary stasis and infection. As indwelling catheters carry higher risk of UTI, condom catheterization is preferred to prevent soiling.
- *Care of bowel* with regular bowel enema in cases with constipation or fecoliths.
- *Care of skin* (frequent sponging), *eyes* (moistening/antibiotic eye drops to prevent exposure keratitis) and *oral cavity* (frequent rinsing), etc.
- *Prevention of contractures* by physiotherapy and splints, etc.
- *Prevention of respiratory complications* with regular chest physiotherapy

c. Monitoring for progression and early detection of complications includes:

- *Continuous clinical monitoring* for depth of coma, vital signs, intake-output chart and complications, e.g. aspiration, infection, bedsores, etc.
- *Periodic electrolyte and arterial blood gas estimations*, specially till stabilization.

d. Treatment of complications:

- *Fluid and electrolyte imbalance:* Regular intake output monitoring, clinical suspicion and periodic electrolyte estimations should guide fluid/electrolyte therapy in comatose child. As SIADH is common, *fluid intake must be restricted to 2/3rd of calculated requirements.*
- *Control of seizures:* Prompt anticonvulsant therapy is essential to prevent seizure-induced brain damage and cerebral edema. Prophylactic anticonvulsants are generally not indicated.
- *Control of raised ICP* by—(a) IV 3% Nacl 0.5–1 ml/kg/hr (with serum sodium monitoring) or IV mannitol 10/20% (0.5–1.0 gm/kg/dose q4–6hr) or (b) steroids, e.g. IV hydrocortisone (100 mg/dose) or dexamethasone (0.2 mg/kg/d q8hr). Therapeutic lumbar puncture or ventricular tap is necessary in some cases.
- *Control of infections* with rational antimicrobials, though prophylactic antibiotics are not necessary.

e. Treatment of primary cause, e.g. infections (antibiotics), poisoning (antidotes, dialysis etc), metabolic problems and liver or renal disease, is discussed in related chapters.

Delirium

Delirium denotes *acute behavioral changes due to neuronal hyperexcitability*, which may be a precursor of coma, though psychiatric problems need to be excluded.

Clinically, these cases present with bizarre behavioral patterns, as follows:

- *Agitation*, i.e. a state of behavioral hyperexcitability with irrational vocalization or motor activity, which is difficult to control.
- *Confusion*, i.e. a state of rapid changes between hyper and hypoexcitability with unpredictable behavior.
- *Delusion*, i.e. fixed beliefs, which cannot be altered with reasoning.
- *Hallucination*, i.e. perception of a sensory stimuli that is not present. Visual hallucinations are mostly organic, while auditory hallucinations usually indicate psychiatric illness or temporal lobe disorders.

Diagnostic evaluation of delirium largely depends on history, as clinical and neurological signs may not be established till the child progress to comatose state.

Some common indicators of probable etiology include:

- Preceding events, e.g. trauma, seizures
- History of exposure to drugs/toxins
- Family history of epilepsy, migraine or psychic illness
- Recent adverse event/conflict at home or school
- Preceding viral illness or systemic disease

Examination of these children should be as elaborate as in comatose child, supported by relevant investigations, before considering the possibility of a psychiatric illness.

18.4 RAISED INTRACRANIAL PRESSURE

Normal intracranial pressure (ICP), as measured in terms of CSF pressure is <10–15 mm Hg. (<7 mm Hg in infants). Raised ICP is both, a *symptom* of serious intracranial pathology, as well as a *cause* of irreversible neurologic injury.

Pathophysiology: Skull is a rigid container, enclosing a fixed volume of brain (80–85%), CSF (10–15%) and blood (5–10%). ICP depends on compliance of cranial vault and volume of intracranial contents. Any increase in intracranial volume is initially compensated by-(a) expulsion of some CSF from intracranial to spinal subarachnoid space, and (b) increase in vault size with bulging fontanels and opening up of sutures (before their closure in infants). When these compensatory limits are crossed, ICP starts rising with following consequences:

- *Compression of intracranial contents*, leading to headache, false localizing signs, e.g. lateral rectus palsy (VI cranial nerve is most susceptible due to longest intracranial course), and autonomic disturbances (brainstem compression).
- *Reduced cerebral perfusion pressure* (<50–70 mm Hg) due to reduced pressure gradient between systemic and cerebral vascular pressure, leading to cerebral anoxia.
- *Herniations*, i.e. shift of the brain structures through various dural openings. Frontal lobes may herniated laterally through Faux cerebri *(trans-faux herniation)*, other supratentorial structures may herniate downward through tentorial notch *(trans-tentorial herniation)* and infratentorial structures may herniated downward through foramen magnum or upward transtentorially. Herniation leads to mass-effect as well as impairment of blood supply to vital structures.

Etiology of raised ICP may be divided into three broad categories—(a) cerebral edema, (b) hydrocephalus, and (c) intracranial space occupying lesions **(Table 18.9)**.

Clinical presentation of raised ICP depends on the primary cause and rapidity of pressure-rise. Important indicators include:

- ***Symptoms:*** (a) Frontal headache, (b) projectile vomiting, (c) diplopia and/or squint, and (d) personality changes, e.g. irritability in chronic case or altered sensorium in acute case. Stiff-neck or head-tilt may be an important indicator of infratentorial herniations.
- ***Neurological signs:*** (a) Increased head circumference, if sutures are open, (b) bulging anterior fontanel,

TABLE 18.9: Causes of raised ICP

- **Increased brain volume**
  - **Cerebral edema**
    - CNS infections: Meningitis, encephalitis
    - Hypoxic brain injury
    - Toxic or metabolic encephalopathies
  - **Intracranial space-occupying lesion (ICSOL)**
    - Brain tumors
    - Infections: Brain abscess, tuberculoma, NCC
    - Intracranial hemorrhage
- **Increased CSF volume**
  - Hydrocephalus
  - Choroid plexus papilloma
- **Increased blood volume**
  - Vascular malformations
  - Cerebral venous thrombosis
- **Limited intracranial space:** Craniosynostosis
- **Others:** Pseudotumor cerebri

TABLE 18.10: Signs of brain herniation

Trans-tentorial herniation

- ***Central*** (diencephalon and midbrain)
  - Altered sensorium
  - Decorticate/decerebrate posture
  - Cheyne-Stokes breathing
- ***Uncal:*** (temporal lobe)
  - Hemiplegia
  - Mydriasis, upward gaze palsy (III cranial nerve)*

Trans-foramen magnum (conal) herniation

- Neck stiffness
- Cardio-respiratory arrest
- Bulbar palsy
- Hypo-/hyperthermia
- Bladder involvement

*similar signs are seen in trans-facial herniations due to unilateral cerebral lesions

(c) *Macewan or crack-pot sign* (signs of sutural diastases), (d) false-localizing signs, e.g. lateral rectus palsy, and (e) signs of brain herniation **(Table 18.10)**.

- ***Papilledema*** **(Fig. 27.1)** is a reliable indicator of raised ICP, though may not appear for many days in acute disease, while chronic cases progress to optic atrophy. Thus, absence of papilledema does not exclude raised ICP.
- ***Signs of autonomic instability***, e.g. (a) bradycardia, (b) hypertension, (c) periodic breathing, and (d) dilated or poorly reactive pupils.

Diagnosis depends on clinical signs, e.g. papilledema *and* high CSF pressure, which may be monitored by invasive spinal/ventricular manometry *or* by non-invasive transcranial Doppler (reduced flow velocity in middle cerebral artery). CT scan may reveal effacement of dorsal peri-mesencephalic cisterns, apart from primary etiology. In cases with normal CT, MRI may be useful to pick up early stroke, venous thromboses and demyelinating lesions.

X-ray skull is abnormal in chronic cases with typical *copper-beaten* or *silver-beaten appearance* **(Fig. 18.1)**.

ICP monitoring is indicated specially in cases with traumatic head injury with GCS score of 3–8, with abnormal CT or motor posturing and hypotension. Benefits of ICP monitoring in other conditions, e.g. intracranial infections and hypoxic-ischemic injuries, are not established.

Management of raised ICP includes:

- **Positioning** in a head-up (~30°) position to encourage jugular venous drainage.
- **Osmotherapy** for the immediate control of ICP with mannitol or hypertonic saline.
  - *IV mannitol* 10–20% (0.25–1.0 gm/kg/dose q8hr) infused rapidly over 15–20 minutes, is generally preferred for this purpose, though prolonged use for >72 hours should be avoided due to risk of rebound rise in ICP, hyovolemia and hypokalemia.
  - *IV hypertonic saline* (0.1 to 1.0 ml/kg/hr) as continuous infusion with target serum sodium level of 145–155 mEq/L) is preferred in cases with hypovolemia or hypotension, which can be used up to 7 days under careful electrolyte monitoring.
  - Milder osmotic diuretics, e.g. *PO Acetazolamide* (50–75 mg/kg/day q8hr) or *PO Glycerol* (1–5 gm/kg/day q6hr) may be used in chronic cases.
- **Hyperventilation** to decrease $PaCO_2$ at ~30–35 mm Hg. Hyperventilation acts by constriction of cerebral blood vessels and lowering of cerebral blood flow. However, vasoconstrictive effect lasts only for 12–24 hours and aggressive hyperventilation can aggravate cerebral ischemia. It is more useful in cases with impending risk of herniation.
- **Steroids,** e.g. IV/PO dexamethasone (0.2 mg/kg/day q8hr) or prednisolone (2 mg/kg/day q8hr) are preferable for long-term use in intracranial infections or space occupying lesions. However, steroids may be detrimental in ischemic lesions, cerebral malaria and intracranial hemorrhage.
- **Surgical intervention,** indicated in life-threatening cases, include—(i) therapeutic lumber puncture or ventricular tapping, (ii) decompression craniotomy with burr-hole, and (iii) removal of subdural hematoma, tumor, etc.
- **Supportive treatment** with control of seizures and primary cause is equally important in these cases.

Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

Idiopathic intracranial hypertension (also termed as *Pseudotumor cerebri*) is a clinical entity, characterized by *transient and unexplained rise in intracranial pressure* (>250 mm Hg) with normal CSF and ventricular size.

Etiology: While exact pathogenesis is not known, pseudotumor cerebri is seen with many conditions

TABLE 18.11: Causes of pseudotumor cerebri

- Hypervitaminosis A or vitamin A deficiency
- Prolonged steroid therapy/sudden withdrawal
- *Drugs:* Nalidixic acid, tetracyclines, nitrofurantoin, etc.
- *Endocrinal:* Addison's disease, hypoparathyroidism
- *Infections:* GBS, otitis media, roseola infantum
- *Vascular:* SVC syndrome, sagittal sinus thrombosis
- *Hematological:* Polycythemia, hemolytic anemia

GBS: Guillain-Barré syndrome, **SVC:** Superior vena caval compression

(Table 18.11), probably due to abnormalities in cerebral blood flow, CSF production or absorption.

Clinically, these cases present with—(a) acute onset of headache, vomiting and diplopia, (b) bulging fontanel, positive *Macewan* sign with/without papilledema, and (c) *absence of* sensorium changes, focal neurological deficits or constitutional symptoms. Spontaneous recovery within 7–10 days without residual sequelae is common though few cases may be left with optic atrophy and impaired vision.

Diagnosis requires exclusion of other CNS disorders by CT/MRI studies.

Management: Pseudotumor cerebri is a self-limiting condition, though severe cases may be treated with repeated therapeutic lumbar punctures and/or PO Acetazolamide (10–30 mg/kg/day q8hr) for 3–5 days or till recovery. Steroids (PO/IV Dexamethasone 0.2 mg/kg/day q8hr) may be used in severe cases.

18.5 HEADACHE

Headache is a common but often under-recognized problem in children, due to their inability to describe it. Head-banging is an important indicator of headache in young children. Though all children occasionally experience headache, recurrent/persistent headache is a cause for concern and needs investigation.

Etiology: Headache disorders in children may be broadly classified as—(a) *Primary (Functional)* headaches, e.g. migraine or tension headaches; (b) *Secondary (Organic) headaches* due to underlying neurological or extra-neurological cause **(Table 18.12)**.

Recurrent headache is more likely to be organic in pre-school children, while psychosomatic headaches are more common in older children. Tension headache is the commonest cause of headache in school age children.

Diagnostic evaluation: A careful history and thorough neurological examination is often enough to differentiate benign headaches from potentially pathological causes. Important diagnostic clues in headache include:

- *Location and character* of headache along with other characteristics, e.g. mode of onset, frequency of attacks, diurnal variation and precipitating/relieving factors.

TABLE 18.12: Causes of headache in childhood

- **Tension/stress headache**
  - Anxiety and stress
  - Occipital neuralgia (unstable atlantoaxial joint)
- **Vascular headache (Migraine)**
- **Intracranial pathology (↑ ICP)**
  - *ICSOL** – tumors, tuberculoma, NCC
  - Infections – meningitis, encephalitis
  - Hydrocephalus/pseudotumor cerebri
  - Cerbrovascular malformations
  - Hypertensive encephalopathy
  - Post-traumatic brain injury
- **Extracranial headache**
  - Ophthalmic – Refractive errors
  - ENT – Chronic sinusitis
  - Dental problems
- ***Psychogenic:*** Conversion reactions, depression
- ***Others:*** Lead poisoning, premenstrual syndrome
- **Idiopathic**

* Intracranial space occupying lesions.

- *Presence of associated complaints*, e.g. vomiting, visual problems or other neurological symptoms.
- *Baseline examination* for refractory errors and ENT check-up including sinus X-rays.
- **Red-flag signs:** Neuroimaging with CT/MRI is indicated only in children with—(a) abnormal neurological signs, (b) recent behavioral changes, (c) and (d) predominantly morning headache with vomiting, (e) papilledema, (f) associated seizures (? AV malformations), and (g) cluster headaches or severe headache during sleep.

Some important causes of headache in childhood are discussed here:

Tension headaches are related to periods of anxiety and stress at home or school, which may unconsciously produce constant isometric contraction of face and neck muscles.

Tension headaches are—*(a) typically dull aching, (b) diffuse or variable in location, (c) more common after or during school hours and (d) not associated with nausea, vomiting* or other symptoms. Persistent spasm of neck muscles indicates possibility of unstable atlantoaxial joint (occipital neuralgia) in some cases.

Diagnosis of tension headache depends on careful history including psychological evaluation and exclusion of other causes. Most cases may be treated with mild analgesics and behavioral therapy.

Intracranial or traction headache indicates raised ICP leading to traction/tension on cerebral vessels or dura matter. These headaches are typically—*(a) common in early mornings, (b) localized in frontal or occipital region, (c) worsen after any activity that further raises ICT*, e.g. *coughing or sneezing, and (d) associated with projectile vomiting, behavioral changes and papilledema*. Diagnosis and treatment depends on individual causative condition.

TABLE 18.13: Diagnostic criteria for migraine in children

a. Recurrent headache with at least > 5 attacks, and
b. Headache lasting for 2-72 hours, and
c. Headache with at least two of the following:
   - Bilateral or unilateral (frontal/temporal)
   - Pulsating quality
   - Moderate to severe intensity
   - Aggravated by routine physical activity
   - Accompanied by at least one of the following:
     - Nausea and/or vomiting
     - Photophobia or phonophobia

Ophthalmic headaches, caused by uncorrected refractive errors, are often difficult to distinguish from tension headaches. These cases usually present with *dull aching frontal headache, more common in evenings and frequent rubbing of eyes*.

Sinus headaches due to chronic ENT problems are common in older children and typically become *more prominent in head-low position like during reading*. Localized sinus tenderness, sinus skiagrams and abnormal ENT findings can establish etiology in these cases.

Migraine: Migraine in children is classified as with or without *aura*, though Migraine without aura is more common in children, characterised by *recurrent headache with at least >5 attacks fulfilling all pediatric migraine diagnostic criteria* ***(Table 18.13).*** History of more than two attacks fulfilling above criteria can also be considered as significant in presence of aura.

Prevalence: Unlike general impression, migraine is not uncommon in children, with estimated incidence of ~4–5% in school-age group and higher (~20–25%) in adolescents, specially girls.

Etiology: Exact cause is unknown, but an inherited predisposition to vasomotor instability appears to be an important underlying factor.

Clinically, most cases of childhood migraine present in early school age with paroxysmal and recurrent attacks of throbbing/pulsating headache associated with vomiting and nausea. Each attack usually lasts for 2–3 hours. *Family history is present in >90% cases.* Characteristic hemicranial distribution and aura, seen in adults, is uncommon in children.

Other variants of migraine present with cyclical vomiting, benign paroxysmal vertigo, acute confusional states or rarely as *complicated migraine* with temporary localizing signs, e.g. alternating hemiplegia, ipsilateral III nerve palsies (ophthalmic migraine), impaired sensorium, vertigo, ataxia and diplopia (basilar migraine).

Diagnosis rests on clinical criteria mentioned earlier, with paroxysmal nature of attacks, positive family history and exclusion of other causes.

Management of migraine includes:

- *Avoidance of precipitating factors*, e.g. stress, fatigue, anxiety, hunger, blinking/bright lights, loud sound and probably certain foods, e.g. Chinese/spicy foods or chocolates.
- *Management of acute attack* with common analgesics, e.g. paracetamol or ibuprofen with/without antiemetics, e.g. prochlorperazine or metochlopramide. *Rizatriptan* (PO 5 mg/dose, repeated in 2 hours to maximum 30 mg/day)-a 5-HT agonists, may be used in children >5 years of age with severe, refractory attacks of migraine. Other triptans, e.g. Sumatriptan, are not recommended in children. IV *Sodium Valproate* 15–20 mg/kg over 10 minutes has been used in adolescents with intractable attacks.
- *Prophylactic therapy* for very frequent and disabling attacks is not standardized in children and includes Propranolol (PO 2–4 mg/kg/day q12hr), Valproic acid (15–30 mg/kg/day q12hr), Flunarizine (5–10 mg/day HS), all taken orally. Topiramate and Amitriptyline may be used on adolescents above 12 years. Cyproheptadine (0.1–0.2 mg/kg BD) may be used in young children. Nutraceuticals, e.g. Riboflavin (25–400 mg/day) and Coenzyme-Q10 (1–2 mg/kg/d) have also shown promising results. Therapy should be continued for 4–6 months before tapering.
- *Behavioral management* and reassurance is needed to relieve the stress and anxiety associated with attacks. History of >2 attacks fulfilling above criteria can also be considered as significant in presence of aura.

18.6 SEIZURE DISORDERS

Seizure is defined as "*transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain*", presenting with motor, sensory, autonomic, or behavioral manifestations. Seizures may be solitary or recurrent. The term seizure disorder denotes all kind of recurrent seizures, and possibly single seizures, irrespective of the etiology.

18.6.1 GENERAL CONSIDERATIONS

Approximately 3–10% of all children are known to experience at least one attack of seizure before 5 years of age, though most of them are benign febrile seizures. Prevalence of recurrent seizures in childhood is ~ 0.5–1.0% and 60% of epilepsies begin in childhood.

Pathophysiology: While precise mechanisms in causation and recurrence of seizures are unclear, three important contributors are:

a. *A group of hyperexcitable neurons*, capable of generating significant burst discharge of electrical activity. Seizures may originate from areas of neuronal death in organic brain lesions that promote development of

hyperexcitable neurons and many epileptic patients are known to benefit from removal of these foci by surgery. Genetic factors account for ~20% of childhood epilepsies, specially myoclonic seizures, e.g. infantile spasms.

b. *Lower threshold of excitatory glutamatergic synapses*, which promote rapid propagation of seizure activity to different areas of brain. Physiological immaturity of developing brain in young children is an important contributory factor in faster propagation of seizure activity.

Repeated sub-convulsive stimulation of the brain, e.g. *Amygdala*, is known to precipitate generalized seizures in experimental studies-a phenomena termed *Kindling*. Recurrent seizure activity from an abnormal temporal lobe may produce seizures from contralateral normal temporal lobe by transmission of stimulus via corpus callosum-a phenomena termed *mirror-image seizure.*

c. *Inadequacy of neuroinhibitory system (Gamma aminobutyric acid or GABA),* responsible for regulation of electric activity. GABA-sensitive *substantia nigra* seems to play an important role in control of seizures, specially in immature developing brain. Although not responsible for onset of seizures, inadequate neuroinhibitory mechanisms are important in development of status epilepticus.

Etiologically, seizures can be broadly classified in three categories **(Table 18.14)**:

TABLE 18.14: Causes of seizures in children

Febrile seizures
Epilepsies and epileptic syndromes
Secondary seizures
- *Infections:*
  Meningitis, encephalitis, cerebral malaria
  ICSOL: Brain abscess, tuberculoma, NCC
  Intrauterine infections
  SSPE, post-viral encephalopathy
- *Traumatic* – head injury, birth trauma
- *Vascular* – strokes, cerebral edema
- *Hypoxic* – ischemic Encephalopathy (HIE)
- *Metabolic:*
  Hypoglycemia
  Hypocalcaemia, tetany, hypernatremia,
  Kernicterus, Reye syndrome
  Pyridoxine deficiency/dependency
  Inborn errors of metabolism, e.g. phenylketonuria
- *Poisoning:*
  Drugs: Aminophylline, phenothiazines, phenytoin
  Poisonings: Lead, strychnine, narcotic withdrawal
- *CNS malformations:* Microcephaly, hydrocephalus
- *Intracranial tumors* (mainly supratentorial)
- *Neurocutaneous disorders:* NF, tuberous sclerosis
- *Functional* (Hysteria)

NF: Neurofibromatosis; **SSPE:** Subacute sclerosing panencephalitis; **ICSOL:** Intracranial space occupying lesions; **NCC:** Neurocysticercosis

a. Febrile seizures due to developmental brain immaturity are commonest but generally benign seizures in pre-school children (Ch 18.6.3).

b. Secondary seizures due to underlying brain pathology or metabolic disorders. This group includes:
- ***Acute symptomatic seizures*** occurring within one week of acute neurological injury, e.g. trauma, stroke, hypoxia, infection or inflammatory pathology and within 24 hours of acute metabolic derangements. These cases require detailed etiological evaluation with serum biochemistry, neuroimaging and CSF examination and short-term anticonvulsant therapy for 6–9 months, apart from treatment of primary cause.
- ***Remote symptomatic seizure*** due to a distant brain injury, e.g. old stroke or structural cerebral lesion, which need long-term anticonvulsant therapy but limited need for investigations.

c. Epilepsy and epileptic syndromes, with enduring predisposition of the brain to generate seizures, discussed later (Ch 18.6.4).

However, this distinction is not mutually exclusive as many cases of febrile seizures or epilepsy are found to have underlying pathology on detailed evaluation.

Clinically, ILAE (2017) broadly classifies seizures as of three types, i.e. those with—(a) focal onset, (b) generalized onset, or (c) unknown onset **(Table 18.15)**.

TABLE 18.15: ILAE 2017 classification of seizures

A. Focal Onset *(with awareness or impaired awareness*)*

Motor Onset
- Tonic, tonic-clonic, clonic
- Myoclonic, epileptic spasms
- Automatisms
- Hyperkinetic

Non-motor onset
- Autonomic
- Behavior arrest, emotional
- Cognitive
- Sensory

Focal-to-bilateral
- Tonic-clonic

B. Generalized onset

Motor
- Tonic-clonic, clonic, tonic,
- Myoclonic, myoclonic-tonic-clonic, myoclonic-atonic
- Atonic
- Epileptic spasms

Non-motor(absence)
- Typical, atypical, myoclonic, eyelid myoclonia

C. Unknown onset
- **Motor:** Tonic-clonic or epileptic spasms
- **Non-motor:** Behavior arrest

D. Unclassified

*at any time during seizure

A. Seizures with generalized onset may be *motor* (tonic-clonic, atonic, myoclonic, epileptic spasms) or *non-motor* (absence).

- ***Tonic-clonic seizures,*** the commonest seizure type, are characterized by four stages, though not necessarily distinguishable in all cases: (a) *Pre-ictal aura,* i.e. premonition of impending seizure, often manifesting as shrill-piercing cry or hallucinations; (b) *Tonic phase,* i.e. sudden contraction of entire musculature with uprolling of eyeballs, clinching of teeth, passage of urine/stools, loss of consciousness and often apnea/cyanosis, lasting for few seconds; (c) *Clonic phase,* i.e. rhythmic contractions and relaxation of muscles for some time before cessation of attack; and (d) *Post-ictal phase* with drowsiness or sleep for few minutes to few hours. Many cases present with either tonic or clonic phase only.
- ***Atonic seizures*** are rare, characterized by sudden and transient loss of body tone with falls, swaying or head drop but *with or without* loss of consciousness.
- ***Myoclonic seizures*** are characterized by sudden, jerky shock like violent muscular contractions with loss of body tone and fall/slump forward.
- ***Epileptic spasms*** are common in infants presenting as startling episodes with sudden flexion or extension movements of head, neck or limbs, usually in clusters.
- ***Absence seizures*** are characterized by sudden cessation of awareness, motor activity or speech for few seconds (<30 sec) without loss of tone; with or without rhythmic movements, e.g. staring spells or fluttering of eyelids, etc. Many such attacks are common in day and may be precipitated with hyperventilation. EEG typically shows 3/second spike and wave activity.

B. Seizures with focal onset usually have an underlying structural cause and are classified as those with (a) *preserved awareness* or (b) *impaired awareness* (previously termed as simple partial and complex partial seizures, respectively). These seizures may be of (a) motor or (b) non-motor onset, e.g. sensory or autonomic seizures. Focal seizures with secondary generalizations (previously termed as Jacksonian march) are termed as *focal to bilateral tonic-clonic seizures*.

Some focal seizures may present as *versive* seizures (tics-like movements, e.g. sudden head turning and conjugate eye deviation) or associated with *automatism,* e.g. lip smacking, chewing, swallowing, pulling on cloths, caressing, nondirective running in fear etc, often misdiagnosed as psychiatric problems.

Status epilepticus (SE), i.e. continuous or sequential seizures lasting for >30 minutes without return of consciousness between attacks, may be the first presentation of seizures or develop during subsequent attacks, discussed later in Ch 18.6.2.

Diagnostic evaluation usually need to be delayed till the control of acute attack, though a quick clinical evaluation with preliminary history and examination helps to arrive at tentative diagnosis and collect relevant laboratory investigations. Important diagnostic clues may be obtained on:

a. Clinical history especially related to:

- Age of onset **(Table 18.16)**
- Type, duration and frequency of seizures
- Associated features, e.g. fever, coma, headache, etc.
- Past history of illnesses, head injury, poisoning, etc.
- Family history of epilepsy, neural tube defects, etc.
- Perinatal history of birth asphyxia, kernicterus, etc.
- History of delayed development
- History of anticonvulsant medication and default

b. General examination especially for:

- Head size, e.g. hydrocephalus, microcephaly

TABLE 18.16: Common causes of childhood seizures according to the age of onset

Newborns (0–30 days)
- *Birth Asphyxia/Injuries:*
  - Hypoxic-ischemic encephalopathy (HIE)
  - Intracranial hemorrhage
- *Metabolic:*
  - Hypoglycemia
  - Hypocalcemia/hypomagnesemia
  - IEMs: Pyridoxine dependency/deficiency
- *Infections:*
  - Neonatal sepsis/meningitis
  - Intrauterine infections
  - Tetanus neonatorum
- Developmental CNS malformations
- Maternal narcotic withdrawal
- Accidental scalp injection of local anesthetics
- Kernicterus

- **1–6 months**
  - *Infections:* Pyogenic meningitis (PyoM)
  - *Metabolic:* Hypoglycemia, hypocalcemia, IEMs*
  - *Hypoxic:* HIE, accidents
  - Developmental CNS malformations
- **6 months–5 years**
  - Febrile convulsions (Commonest)
  - *Infections:* PyoM, TBM, encephalitis, C. malaria
  - *ICSOL:* Tuberculoma, NCC, brain tumors
  - *Traumatic:* Head injury
  - Cerebrovascular accidents/strokes
  - Toxins and poisonings
  - *Others:* Neurodegenerative/neurocutaneous disorders
  - Idiopathic epilepsy
- **Beyond 5 years**
  - All above (C) except typical febrile seizures

*Inborn errors of metabolism, e.g. Phenylketonuria, **NCC:** Neurocysticercosis; **PYOM:** Pyogenic meningitis; **TBM:** Tubercular meningitis; **ICSOL:** Intracranial space occupying lesions

- Neurocutaneous markers
- Organomegaly, e.g. in intrauterine infections or storage disorders

c. CNS examination after post-ictal phase for:

- State of sensorium
- Signs of meningeal irritation, raised ICP
- Focal neurological deficit
- Fundus examination

d. Laboratory investigations depend on probable cause, though most cases require following basal investigations at the time of first attack, *except* very typical cases of simple febrile seizures.

- *CSF examination* to exclude meningitis.
- *Neuroimaging* with CT/MRI.
- *EEG* with activation procedures, e.g. sleep deprivation or photic stimulation. However, normal EEG does not exclude epilepsy, while it may be transiently abnormal even in simple febrile seizures.
- *Biochemical investigations* for Blood sugar, S. ca^{++}, Mg^{++}, especially during first attack in infants, in whom metabolic seizures are common.
- *Other investigations*, e.g. metabolic screening for inborn errors, are indicated in selected cases.

Management of seizure disorders may be divided into—(a) control of acute attack, (b) long-term anticonvulsant therapy and (e) treatment of underlying pathology.

I. Emergency management: All seizures are potentially life-threatening events and emergency management of acute attack or status epilepticus includes:

A. Basic life support:

- Loosening of tight garments and removal of sharp harmful objects from vicinity to prevent injury
- Recovery positioning with head turned to one side to prevent aspiration
- Restoration of airway (suction) and oxygen administration for prolonged seizures
- Transportation to equipped intensive care

B. Supportive therapy in intensive care:

- Breathing support with oxygen *or* bag and mask ventilation, as necessary
- IV access for circulatory support
- Collection of samples for blood sugar, S.Ca^{++} and anticonvulsant drug levels (if on treatment).
- Quick clinical evaluation for probable cause

C. Specific anticonvulsant therapy is the first priority in all seizures, irrespective of etiology, using a step-wise approach as shown in **(Table 18.17)**.

However, in strongly suspected metabolic seizures (apparently normal newborns or infants < 3 months) with first attack of short-duration seizure (<10 minutes) and no other neurological signs, a sequential therapeutic trial of IV dextrose and calcium gluconate administration after sample collection for biochemical studies, may be attempted to exclude metabolic seizures (Ch 12.16).

TABLE 18.17: Step-wise anticonvulsant therapy for acute seizures/status epilepticus

Step I (Immediate, 0–5 min)
- IV Lorazepam 0.1 mg/kg @ 2 mg/min (max 4 mg) or
- IV Diazepam 0.2 mg/kg slowly (or PR* 0.5 mg/kg) or
- IV Midazolam 0.2 mg/kg slowly (max 5 mg) (or IM/nasal/buccal*)

(*if IV access is not available)

Step II (5–20 minutes)
- IV Fosphenytoin 20 PE/kg @ 3 mg PE/kg/min or
- IV Phenytoin 20 mg/kg in 1:1 NS @ 1 mg/kg/min
- (can repeat Phenytoin/ Fosphenytoin 10 mg/kg or equivalent once)

Step III (No response to step I-II and PICU not available)
- IV Valproate 20 mg/kg in 1:1 NS, @ 6 mg/kg /min, or
- IV phenobarbital 20 mg/kg in NS @ 1.5 mg/kg/min, or
- IV Levetiracetam 20–30 mg/kg @ 5 mg/kg/min, with
  - Monitor Airways, Breathing, Circulation
  - Shift to the PICU, as early as possible

Step III (No response to step I-II and PICU facility available)
- IV Midazolam infusion (0.2 mg/kg(L) > 0.1 mg/kg/h)
- (titrate up every 15 min by 0.05 mg/kg/hr till max 2 mg/kg/hr) or
- IV Propofol / Ketamine infusion (To be avoided)

Step V (no response to step IV)
- General anesthesia with ventilatory support

PE: Phenytoin equivalent
Caution: Use half of the loading dose is already on same drug
Avoid Valproate in liver disease, children < 2 years
Avoid Levetiracetam in renal failure. Preferred in metabolic disorders
Avoid benzodiazepines in liver disease, neuromuscular disorders

II. Long-term anticonvulsant therapy (ACT): Each attack of seizure may lead to further worsening of neurological injury and increased chance of recurrence. Long-term ACT *aims* not only to prevent recurrence of seizures but also to improve quality of life and requires understanding of following facts:

- When to start ACT?
- Which drugs to be used?
- How to monitor and modify ACT?
- How long to continue ACT?

When to start ACT? All cases of recurrent seizures do not require prolonged ACT. Long-term ACT is not indicated in simple febrile seizures, benign myoclonus of infancy and in most cases of *Rolandic* epilepsy. Non-epileptic seizure-like disorders, e.g. syncope, breath-holding spells and benign paroxysmal vertigo must be excluded before initiating ACT.

While there is no uniform agreement, ACT may also be withheld from a previously healthy child with first afebrile seizure, provided—(i) family history is negative, (ii) clinical examination and EEG is normal and (iii) family is cooperative and compliant for follow-up.

TABLE18.18: Common anticonvulsant drugs used in children

Drug	*Initial (Loading) dose*	*Maintenance dose*	*Side effects*
Sodium channel blockers			
Phenytoin	20 mg/kg	3–8 mg/kg/day**	Gum hyperplasia, ataxia
Carbamezapine	-	10–20 mg/kg/day**	Ataxia, hepatotoxicity
Valproic acid	10 mg/kg	15–60 mg/kg/day**	Hepatotoxicity
Lamotrigine	-	10–15 mg/kg/day**	Rash (3–5%), ataxia
Lacosamide	-	4–12 mg/kg/day	Dizziness, liver dysfunction
Chloride channel facilitators			
Phenobarbitone	20 mg/kg	3–5 mg/kg/day**	Behavior/learning problem
Clonazepam	0.05 mg/kg	0.1–0.2 mg/kg/d***	Sedation, behavior problem
Nitrazepam	0.2 mg/kg	0.25–1 mg/kg/d***	Same as above
Clobazam	0.25 mg/kg	0.5–1.0 mg/kg/d***	Same as above
Lorazepam	0.05–0.1 mg/kg	0.05–0.1 mg/kg**	Same as above
Calcium channel blockers			
Ethosuximide	20 mg/kg	40 mg/kg/d**	Rash, leukopenia
Topiramate	1–3 mg/kg	1–9 mg/kg/d**	Cognitive dysfunction
Synaptic vesicle protein (SV2A) binder			
Levetiracetam	20–30 mg/kg	20–40 mg/kg/d**	Psychiatric problems
Increase neuroinhibitory GABA levels			
Vigabatrin	50 mg/kg	50–100 mg/kg/d**	Hyperactivity, optic damage
Gabapentin	–	20–50 mg/kg/d***	Ataxia, tremors
Carbonic Anhydrase inhibitor			
Zonisamide	2 mg/day	2–12 mg/day	Hepatic impairment

/*indicates number of divided doses/day, i.e.**(2 divided doses),***(3 dividedd oses)

However, all cases with second attack of any afebrile seizure (barring above mentioned benign conditions) need to be started on long-term ACT.

Which drugs to be used? A plethora of antiepileptic drugs **(Table 18.18)** are available and the choice depends on the type of seizures as well as other factors, e.g. age, safety profile, drug-interactions and therapeutic response to previously used drugs. Antiepileptic drugs act by interfering with the sodium, potassium or calcium ion channels to reduce excitatory neurotransmitter release or function, or by enhancing GABAergic inhibition. Preferred choice of drug/s in various seizure/epilepsy types is discussed in Ch 18.6.4. Certain general principles need to be remembered while using antiepileptics:

- Single drug therapy is preferable to polytherapy, which should be used only in refractory cases.
- Each drug should be started with lowest recommended dose and increased gradually at weekly intervals till seizures are controlled. Most anticonvulsants take ~1 week to achieve sustained blood levels, necessary for seizure control.
- Compliance should be assured before considering a drug as *ineffective*. Timing of drug ingestion is also important, as absorption of most anticonvulsants is hampered with presence of food in stomach.
- If the seizures are not controlled even with highest dose of single drug, second drug may be added with lowest possible dose and increased gradually.
- Control of seizure after addition of second drug indicates its efficacy and then the first drug may be gradually tapered-off, under close monitoring.

Monitoring and modification of ACT: All cases on ACT should be monitored periodically for control of seizures, adverse effects of drugs and progression of primary lesion. Occasional break-through seizures are not uncommon even in well-controlled children, especially during fever and do not warrants change of ACT.

However, recurrent seizures despite ACT indicate need to review the-(a) compliance, (b) adequacy and timing of the dose, (c) therapeutic drug monitoring for serum levels.

Therapeutic drug monitoring (TDM) is an excellent tool to differentiate drug failure from poor compliance. Sub-therapeutic drug levels indicate need to ensure compliance rather than change of drug. However, recurrence of seizures despite adequate serum drug levels warrants either substitution with second-line drugs or addition of adjuvant drugs (*polytherapy*)

How long to continue ACT? Most seizures recur within first month (60%) and chances of recurrence decline with increasing seizure-free interval. Risk of recurrence in absence of active or structural brain lesion is almost nil after 2–3 years.

Hence, ACT should be continued till at least-(a) two years after the last seizure, (b) EEG is abnormal, and (c) primary lesion is structural or active, likely to cause recurrence of seizure. ACT drugs should be withdrawn slowly, one at a time, to prevent sudden recurrence. In severe epileptic syndromes, e.g. mesial temporal sclerosis or Lennox-Gastaut syndrome, longer or even life-long therapy may be required while in acute symptomatic seizures or benign epileptic syndromes the duration of ACT therapy can be as short as 6–9 months.

18.6.2 STATUS EPILEPTICUS

Status epilepticus (SE) refers to a *single or recurrent seizures lasting for >30 minutes during which the patient does not regain consciousness.* However, a seizure that last for >5 minutes is unlikely to stop spontaneously and needs intervention. Hence, an *operational definition* has been suggested for SE in children above 5 years as "*more than 5 minutes of continuous seizures or two or more discrete seizures, without regaining consciousness*".

ILAE defines SE "as a condition due to either failure of the mechanisms to terminate the seizures or initiation of mechanisms which lead to abnormal prolonged seizures (after time-point **t1**), which can have long-term consequences (after time-point **t2**) including neuronal death, neuronal injury or alteration of the neuronal networks depending on the type and duration of seizures".

Most common with generalized tonic-clonic seizures, status epilepticus may develop with any seizure type, e.g. absence seizures, partial seizures (*Epilepsia partialis continua*), myoclonic seizures, and even febrile seizures (*Status febrilis*). However, time-point **t1** and **t2** differ with type of seizures, being 5 and 30 minutes respectively for generalized seizures, 10 and 60 minutes for focal seizures and 15 and 60 minutes (or unknown) for absence seizures.

Pathophysiology: SE indicates either *persistence of neuroexcitatory influences* (principally mediated by acetylcholine, glutamate or aspartate) or *failure of neuroinhibitory mechanisms*, (principally mediated by gamma-aminobutyric acid or GABA).

Studies have shown that continued seizure activity beyond 30 minutes (transitional period) leads to significant changes in cerebral blood flow, lactic acidosis, altered blood–brain barrier, elevation of intracranial pressure, hypoglycemia and autonomic dysfunction-ultimately leading to irreversible neurological damage.

Clinically, while SE usually develops in a known case of seizure disorder following sudden withdrawal of anticonvulsants, sleep deprivation or intercurrent infections, it may be first manifestation of underlying structural or metabolic abnormality in > 30% cases.

Management of SE, though more intensive, is principally similar to that of acute seizures, **(Table 18.17)**. Broadly, it involves *initial therapy* usually with Benzodiazepines, followed by *urgent therapy* with Fosphenytoin/Phenytoin, Valproate, Phenobarbitone or Levetiracetam.

Refractory SE, which fails to respond to two drugs, needs to be treated in intensive care with continuous infusion of midazolam, Propofol or Ketamine. Some cases need general anesthesia with ventilator support. SE, which does not respond despite 24 hours of anaesthesia is termed as *super-refractory*.

Outcome: SE, specially of convulsive type, is associated with high mortality (~10%) or irreversible neurological damage (~10%) due to prolonged cerebral hypoxia and other factors. Risk of recurrence is as high as 25–75%.

18.6.3 FEBRILE SEIZURES

Febrile seizures (FS) are commonest cause of seizures in pre-school children, associated with any fever of non-CNS origin, excluding intracranial pathology, e.g. CNS infections. However, all seizures with fever are not febrile seizures.

Cardinal features of a typical FS include:

- Age group-6 months to 5 years,
- Presence of fever >38°C, and
- No evidence of pre-existing or post-ictal neurological deficit *except* transient drowsiness or Todd's palsy for 24 hours in some cases.

Some guidelines include diagnosis of FS even in younger infants (< 6 months) after excluding other causes of provoked seizures.

Incidence: One or more attack of FS are experienced by ~4–5% of all children <5 years of age, more common in boys.

Family history is present in ~30% cases and genetic predisposition is known involving many genes, including $FEB_{1–10}$ genes. Many epileptic syndromes with established genetic basis, e.g. Dravet syndrome, are known to present with FS in early stages.

Pathogenesis: Exact pathogenesis of FS is not unclear, but probably relates to developmental immaturity of brain with lower threshold for neuroexcitation in response to fever due to hyperthermia induced brain alkalosis and perturbation of temperature sensitive ion channels. Interleukin-1β, a pyrogen, also acts as seizure provocator through glutamate pathway.

TABLE 18.19: D/D Simple vs complex febrile seizures

Character	*Simple FS*	*Complex FS*
Type of seizure	GTC	Focal
Duration	<15 minutes	> 15 minutes
Frequency/24 hours*	1	> 1
Prognosis	Excellent	Poor

* or per febrile episode

Clinically, FS usually develop within 24 hours of onset of any non-specific febrile illness in susceptible age group, usually during rising phase of fever. While fever is an essential criteria, magnitude of fever is perhaps less important than the rate of temperature rise.

Depending on clinical presentation and prospective outcome, FS are divided into two distinct categories-simple and complex FS **(Table 18.19)**.

- ***Simple febrile seizures*** (SFS) are almost always benign with following characteristics—(a) generalized, (b) short-lasting <15 minutes, and (c) do not recur during same episode or within 24 hours. Most episodes occur during first 24 hours of onset of febrile illness. EEG beyond 2–3 weeks in these cases is essentially normal and risk of secondary epilepsy is almost nil.
- ***Complex febrile seizures*** (CFS) account for ~15–20% of all FS, which may be—(a) focal, (b) prolonged >15 minutes, and/or (c) recur within 24 hours. CFS are more common in older children and many of them begin as SFS during initial episodes. CFS are more likely to have underlying brain pathology, abnormal EEG and risk of recurrence or secondary epilepsy.

Febrile seizure plus refer to FS, which—(a) continue past the usual age when they are expected to resolve (6 years) ***and/or*** (b) accompanied by afebrile generalized (tonic-colic, myoclonic, absence) or focal seizures.

Febrile status (Status febrilis) denotes persistence of FS for >30 minutes, either single or recurrent without regaining consciousness.

Diagnosis of FS is mainly clinical and detailed investigations are unnecessary in most cases, especially on subsequent attacks. However, since it is difficult to exclude intracranial pathology during first attack, following investigations are recommended in selected cases:

- ***CSF examination*** must be considered during first attack in all cases <12 months of age *and* in older children only if they appear ill or pre-treated with antibiotics. Repeat lumbar puncture is not necessary during subsequent attacks, unless strong evidence of intracranial infections is present.
- ***EEG:*** Although of doubtful value in neurologically normal cases (abnormal EEG does not predict risk of epilepsy), EEG is advisable in cases with CFS or focal findings on neuroimaging within one week of seizure.
- ***Neuroimaging*** with CT/MRI is not routinely indicated, unless abnormal neurological signs are present. Emergency CT without contrast is indicated in cases with status epilepticus, history of trauma, signs of raised ICP and underlying CSF shunt. MRI must be considered only after stabilization in children with febrile status epilepticus or prolonged/focal CFS to rule out underlying pathologies.
- ***Other investigations***, e.g. blood sugar and serum calcium estimation may be considered in infants, as also the sepsis screening. Genetic testing for Dravel syndrome is indicated in cases with recurrent febrile status epilepticus

Management of FS involves: (a) management of acute attack, and (b) prevention of recurrence during subsequent febrile episodes.

a. Management of acute attack: FS usually develop at home. Parents must be reassured about the benign nature of these episodes and trained to manage them at home as follows:

- Control the acute seizure with intranasal Midazolam (0.2 mg/kg), to be given within 3–5 minutes of the onset and repeated after 5 minutes in case of persistent seizure. Midazolam is preferred over per rectal diazepam.
- Place the child in recovery (Lateral) position to prevent aspiration.
- Control the fever with hydrotherapy (cold-sponging) and antipyretics (paracetamol). Antipyretics decrease the discomfort but do not reduce the risk of recurrence of FS.
- Visit the nearest health facility if—(a) it is first attack, (b) seizures are not controlled with two doses of abortive medication, i.e. midazolam, or (c) child remains in postictal phase for long.

Treatment of FS in hospital must follow standard guidelines for management of status epilepticus (Ch 18.6.2), along with diagnosis and treatment of the cause of fever.

Prophylactic antibiotics, e.g. a third generation cephalosporin may be started in young infants with clinical suspicion of meningitis till CSF results.

b. Prevention of recurrence: Early recognition and treatment of febrile illness with antipyretic therapy is the key to prevent recurrence in FS, which is common in ~30–40% cases. Exact role of prophylactic anticonvulsants in these cases is controversial, generally not recommended in children with one or more simple FS. Anticonvulsant therapy *in FS may prevent the recurrence but does not reduce risk of subsequent epilepsy*.

Common practices for FS prophylaxis are:

- ***Intermittent anticonvulsant prophylaxis*** with PO Clobazam (0.5–1 mg/kg/day q12hr) during first 3 days of a febrile episode (>38°C), which may be used in cases with: (a) high-risk of recurrence (*see* below outcome), or (b) high parental anxiety, or

(c) residence far away from medical facility, or (d) CFS not on continuous prophylaxis. However, most FS develop during first few hours of febrile illness, which may not be recognized. Intermittent prophylaxis is not recommended for the first episode of SFS.

- ***Continuous anticonvulsant prophylaxis*** is indicated *only* in cases with—(a) febrile status epilepticus, (b) neurodevelopmental delay, and (c) frequent CFS, and (d) febrile seizure plus/GEFS with afebrile seizures. *Sodium valproate (PO 20–40 mg/kg/d q8hr)* is the drug of choice for this purpose, as phenobarbitone affects cognitive function and phenytoin or carbamazepine are less effective. Once started, prophylaxis should continue for minimum 2 years.
- ***Antipyretic medications***, e.g. Paracetamol 15 mg/kg/dose every 6 hours may be advised in all cases during the febrile episode, to make the child comfortable. However, this practice of round-the-clock antipyretics do not prevent occurrence/recurrence of FS.

Outcome: SFS are almost always benign, remitting spontaneously after 5 years of age with ~1% risk of developing epilepsy and no late-effect on intellectual or motor functions. However, risk of *recurrence in SFS is ~75% within a year after the first episode, higher* in those with (a) early age of onset < 18 months, (b) family history of FS/epilepsy, and (c) shorter duration of fever before seizure < 1 hr and d) seizures with low-grade fever (<39°C).

Children with (a) CFS, (b) family history of epilepsy, or (c) associated neurological abnormalities/developmental retardation, carry higher risk of recurrence as well as development of epilepsy, i.e. 5–50% depending on the number of complex features.

Generalized epilepsy with febrile seizure plus (GEFS$^+$) is an autosomal dominant syndrome with highly variable phenotype. Most cases present in early childhood with multiple febrile seizures, later followed by multiple types of afebrile generalized seizures with variable phenotypes. Remission is common by mid-childhood. A family history of FS is present.

Dravet syndrome is the most severe type of febrile seizure-associated epilepsies, usually due to *de novo* mutation (2q24–31). These cases present in early infancy with prolonged and focal clonic febrile seizures, often in clusters, recurring every 1 or 2 months. Later, seizures start to occur without fever and become more variable in phenotype, e.g. myoclonus, atypical absences, and partial seizures. Developmental delay is common. Milder variants are referred as *Dravet syndrome spectrum*.

18.6.4 EPILEPSY IN CHILDHOOD

Epilepsy, according to International League Against Epilepsy (ILAE) is defined as:

- At least two unprovoked (or reflex) seizures, at least 24 hours apart;
- One unprovoked (or reflex) seizure and probability of further seizures similar to general recurrence risk (at least 60% after two unprovoked seizures), over next 10 years;
- Diagnosis of an epilepsy syndrome.

In practice, clinical diagnosis of epilepsy requires occurrence of at least one unprovoked seizure with either a second seizure after at least 24 hours *or* an EEG abnormality to suggest predisposition for recurrence.

Epilepsy syndrome refers to "*a constellation of signs and symptoms that often occur together, such as seizure type, age of seizure onset, responsiveness to certain anti-seizure drugs, and characteristic EEG findings, underlying genetics, and natural history.*"

Epileptic encephalopathy denotes *an epileptic condition associated with progressive cerebral dysfunction or delay, behavioral or cognitive issues*, e.g. West syndrome, Lennox-Gastaut syndrome, etc.

Etiologically, epilepsy in children has been broadly classified as of—(a) genetic, (b) structural, (c) metabolic, (d) infectious, (e) immunological, and f) unknown origin, according to ILAE 2017 classification.

Genetic epilepsy (previously termed as Idiopathic) refers to an underlying known or presumed genetic defect, which is not causative of a brain structural or metabolic disorder other than the epilepsy. Other etiological types of epilepsy (except unknown) denote presence of an underlying cause (secondary epilepsy).

Some important and common types of epileptic presentations and related syndromes are as follows:

Generalized tonic-clonic seizures (Grandmal epilepsy) are the commonest seizure type in childhood, which may occur *de novo* or follow a partial seizure with secondary generalization (*Jacksonian march*). While most cases of these seizure types have an underlying pathology and tend to recur, single isolated seizure is not uncommon during an intercurrent illness with unidentified etiology.

Absence seizures (Petit mal Epilepsy) are characterized by sudden cessation of motor activity or speech for few seconds (< 30 sec) only, with/without rhythmic movements, e.g. fluttering of eyelids, etc.

Typical absence seizures usually start at 5–8 years of age, more common in girls. Aura and post-ictal phase is absent. Muscle tone and posture is well preserved. Frequency may vary from few to countless attacks per day, sometimes presenting with *absence status epilepticus.* Absence attacks may be precipitated by hyperventilation for 3–4 minutes.

Etiology is generally idiopathic, but learning and behavioral problems are common. Early-onset seizures (<4 yrs) may be associated with a glucose transporter defect. *EEG is characteristic with a 3/seconds spike and slow wave pattern.* While ~50% cases become seizure-free after

some time, rest may develop into tonic-clonic attacks, specially those with very early or late onset.

Atypical absence seizures have associated myoclonic component and tone changes, e.g. *head drop*, sometimes precipitated by drowsiness. EEG may show 1–2 Hz spike and slow wave discharges.

Juvenile absence seizures are similar to typical absence seizures but occur at a later age, often associated with juvenile myoclonic epilepsy. EEG may show 4–6 Hz spike and slow wave discharges.

Myoclonic seizures are characterized by rapid, brief, repetitive *but not rhythmic*, muscular contractions with loss of body tone and fall/slump forward. Etiological spectrum of myoclonic epilepsy spans from essentially benign seizures, e.g. *benign myoclonus of infancy* to severe intractable disorders, e.g. *Lennox-Gastaut syndrome*. Some common myoclonic syndromes are as follows:

Infantile spasms is the commonest myoclonic epilepsy, beginning at the age of 4–8 months.

Clinically, infantile spasm is characterized by clusters of brief symmetric myoclonic contractions of neck, trunk and extremities, with three variants—(a) *Flexor spasms*, with sudden flexion of neck, arms and legs onto the trunk *(salaam spells);* (b) *Extensor spasms*, with sudden extension of trunks and extremities (least common); and (c) *Mixed*, with flexor and extensor spasms during different clusters. Most clusters last for few minutes and usually seen in early mornings. EEG in infantile spasm is generally characteristic, revealing *hypsarrhythmia,* i.e. a chaotic pattern of high voltage, asynchronous slow wave activity with superimposed spike waves.

Etiologically, infantile spasms are either *cryptogenic* (10–20%) without identifiable cause or *symptomatic* (80–90%) following birth asphyxia, intrauterine infections, perinatal meningitis, neonatal hypoglycaemia, head trauma and developmental CNS malformations. DPT immunization, once implicated etiologically, probably has no cause effect relationship.

Pathogenesis is unclear, though it has been suggested that perinatal stress during critical period of neurodevelopment leads to overproduction of corticotrophin release hormone (CRH), which may induce neuronal hyperexcitability. CRH suppression with exogenous ACTH/steroids has been found effective in control of infantile spasm.

Management: ACTH therapy is the drug of choice for infantile spasms given intramuscularly as 6 units/kg/day for 2 weeks, which must be tapered over next 2–4 weeks, depending on the clinical and EEG response. Alternatively, high dose oral prednisolone (4 mg/kg/day) may be used with similar schedule.

Vigabatrin is the drug of choice for infantile spasms in children with tuberous sclerosis, while it may be used as second-line drug or adjuvant in other cases. Other alternatives include Benzodiazepines or Valproic acid.

Outcome and therapeutic response is better in cryptogenic cases, while those with underlying neuropathology tend to be refractory with ~80% risk of mental retardation.

West syndrome is a triad of infantile spasms, developmental regression and hypsarrhythmia on EEG. Etiologically, while many cases are cryptogenic (unknown etiology) with normal development before the onset of spasms, others may have significant underlying pathologies, e.g. perinatal encephalopathies, brain malformations, metabolic disorders, etc. In boys, some cases may be associated with *ARX* gene mutations, along with ambiguous genitalia and cortical migration defects.

Benign myoclonus of infancy usually begins in late infancy with clusters of myoclonic seizures, which disappear spontaneously at ~2 years. EEG is usually normal or shown non-specific abnormalities (d/d infantile spasms). No treatment is necessary.

Typical myoclonic epilepsy of early childhood begins at ~1–4 year with variable frequency of myoclonic and generalized tonic-clonic seizures. Family history of similar seizures and past history of complex febrile seizures is common. EEG usually reveals *fast spike-wave complex at >2.5/sec with normal background* rhythm. While most cases become seizure-free after few years, learning and behavioral disorders are common.

Juvenile myoclonic epilepsy *(Janz syndrome)* is the commonest generalized epilepsy in young adults, with usually autosomal dominant inheritance, linked to mutations in many genes (e.g. CACNB4).

Clinically, JME presents in early adolescence with early morning myoclonic seizures, often causing the patient to drop things. Seizures are more common in sleep-deprived individuals and usually abate as the day progresses. Some cases may develop early-morning generalized tonic-clonic seizures, when awakened suddenly. EEG shows *4–6/seconds irregular spike and wave pattern,* which enhances on photic stimulation.

CNS examination and MRI is normal and seizures responds well to *sodium valproate*, though *life-long* therapy is necessary to prevent recurrence. *Lamotrigine* is the alternative, specially preferred in adolescent girls. Carbamazepine and Phenytoin may worsen the symptoms.

Lennox-Gastaut syndrome typically starts at 2–10 years of age with a characteristic triad of—(a) intractable seizures of various types, e.g. tonic, myoclonic, atonic and a typical absences, (b) mental retardation, and (c) typical EEG findings with slow spike-wave (< 2/sec) discharges. These seizures are often *secondary* to diffuse infective or hypoxic encephalopathies and *refractory* to multiple anticonvulsants. Most cases are left with long-term cognitive impairment and intractable seizures despite multiple therapies.

Atonic seizures are rare and characterized by sudden and transient (1–4 seconds) loss of body tone with frequent falls, swaying or head drop; without loss of consciousness. These seizures usually begin at ~1–3 years and underlying brain disorders (e.g. Tuberous sclerosis) and mental retardation is common.

Focal (partial) seizures may be with/without loss of consciousness and with/without *secondary generalization.* Focal seizures usually indicate symptomatic epilepsy due to underlying disease, e.g. brain malformations, tumors, hypoxic–ischemic injury or severe metabolic disease and tend to be more severe and refractory to the treatment. Some common epileptic syndromes with predominantly focal seizures are as follows:

Self-limited epilepsy with centrotemporal spikes (previously termed as benign rolandic epilepsy) typically starts at ~10 years of age in previously normal children, with strong family history.

Clinically, child typically wakes up at night usually within 1–2 hours of falling asleep or prior to awakening, with a focal seizure involving facial twitching and oropharyngeal symptoms, e.g. tongue paresthesia, dysarthria and excessive salivation. Consciousness is generally preserved though secondary generalization may occur.

EEG is characteristic with *broad-based centrotemporal spikes from a rolandic focus, specially during drowsiness and sleep with normal background activity.*

Most cases remit spontaneously by 15–16 years of age and anticonvulsant therapy (preferably with carbamazepine) is indicated only in cases with recurrent troublesome seizures.

Self-limited epilepsy with autonomic features (previously termed as benign epilepsy with occipital spikes) may begin in early childhood at 3–5 years of age, with complex partial seizures and vomiting, retching, pallor, flushing and abdominal pain. Episodes usually remit in few years.

Childhood onset visual epilepsy (COVE) presents in school age group of 6–14 years, with seizures characterized by focal sensory visual phenomena like multicolored circles with/without deviation of eyes with/without impaired awareness.

Mesial temporal sclerosis presents as temporal lobe epilepsy, often preceded by febrile seizures. Pathologically, these patients have atrophy and gliosis of the hippocampus and amygdala. Sometimes, focal discharges may be continuous to cause epileptic encephalopathy. Activation of temporal discharges in sleep can lead to loss of speech and verbal auditory agnosia (**Landau-Kleffner syndrome**). Treatment is mainly medical but surgical treatment may be necessary in refractory cases.

Reflex seizures: Many patients get seizures only in response to a very specific, identifiable sensory stimulus and these seizures are termed as reflex seizures. Sensory stimuli may be external (flickering light, loud music or sound, hot-water, etc.) or internal (reading, thinking, calculation, etc.).

Clinically, reflex seizures may be generalized, partial, non-convulsive, absence or myoclonic. Photosensitive seizures are commonest types of reflex seizures, often triggered by bright or flashing lights, e.g. TV, video games, discotheques, etc. Photomyoclonic seizures often present with forehead muscle twitching or repetitive eye blinking.

EEG may be normal or abnormal on photic stimulation. Patients tend to outgrow photosensitive seizures by 30–40 years of age. Avoidance of stimuli is usually enough in most cases while some may need anticonvulsant therapy, preferably with valproic acid.

Management of Epileptic Disorders

Management of epileptic disorders may be broadly divided into four components:

A. Control of acute attack or status epilepticus, as discussed in Chapter 18.6.1, **Table 18.4**.

B. Long-term anticonvulsant therapy, based on the principles discussed earlier (Chapter 18.6.1), though the choice of anti-epileptic drugs (AEDs) vary according to the type of seizures and therapeutic response **(Table 18.20)**.

Apart from established AEDs, others, e.g. steroids and IV immunoglobulins are also used in selected cases. *Steroids* (ACTH or Prednisone) are used in epileptic encephalopathies, e.g. infantile spasms, West syndrome, Lennox-Gastaut syndrome, etc. *IV Immunoglobulins are* used in West syndrome, Lennox-Gastaut syndrome, Landau-Kleffner syndrome, etc.

Mechanism of action of steroids and of IVIG is not known, presumed to be anti-inflammatory by reducing seizure-induced cytokine levels, which tend to increase neuronal excitability. Steroids might also stimulate brain neurosteroid receptors to enhance GABA activity and reduce corticotrophin-releasing hormone, which is known to be epileptogenic.

TABLE 18.20: Long-term ACT of choice in seizure disorders

Seizure types	*First choice*	*Alternatives*
GTC	VAL, PHT	LEV, LTG
Absence	VAL, LTG	LEV, TPM, ZNS
Focal	OXC/CBZ	VAL, PHT
Myoclonic	VAL	LEV, TPM, ZNS
Infantile spasms	ACTH	VGB
Lennox-Gastaut	VAL, LTG	LEV, CLB, TPM, ZNS

ACTH: Adrenocorticotropic hormone; **CBZ:** Carbamazepine; **CLB**: Clobazam; **CLZ:** Clonazepam; **ETHX:** Ethosuximide; **LEV:** Levetiracetam; **LTG:** Lamotrigine; **OXC**: Oxcarbazepine; **PHB:** Phenobarbitone; **PHT:** Phenytoin; **TPM:** Topiramate; **VAL:** Valproic acid; **VGB:** Vigabatrin; **ZNS:** Zonisamide

C. Non-pharmacological interventions, e.g. surgery or dietary modifications (e.g. ketogenic diet) are of limited value in epileptic children.

***Surgery** is* rarely indicated in childhood epilepsy except select cases of refractory seizures, which involve-ablation of identified epileptic foci (stereotactic surgery), partial excision of affected lobe or resection of corpus callosum to prevent spread of electrical activity. Surgery should be considered only in cases with—(a) documented failure of medical therapy with minimum three anticonvulsants in maximum permitted doses, (b) a properly defined *epileptogenic zone*-area that needs to be resected to achieve seizure freedom and (c) unlikelihood of unacceptable adverse consequences of surgery.

Ketogenic diet has been used for refractory seizures of various type, e.g. infantile spasms, tuberous sclerosis complex, Dravet syndrome and some mitochondrial disorders. It involves an initial period of fasting followed by a diet with Fat:Non-fat ratio of 3–4:1 and fats consisting of animal fat, vegetable oils, or medium-chain triglycerides. Ketogenic diet is contraindicated in carnitine deficiency and other metabolic epileptic disorders. Diarrhea, vomiting, hypoglycemia and dehydration is common with these diets along with poor palatability.

D. General supportive care in children with seizure disorders includes—(a) psychological support and counseling, (b) accident prevention, (c) educational modifications, and (d) rehabilitation.

18.6.5 SEIZURE-LIKE DISORDERS (SEIZURE MIMICS)

Many conditions present with paroxysmal seizure-like episodes without true epileptic activity but easily confused with seizures. Anticonvulsants have no role in these cases. Some important non-seizure paroxysmal disorders are as follows:

Syncope may be defined as "*transient loss of consciousness due to sudden alterations in cerebral blood flow or brain metabolism*", with or without seizure activity, flaccidity and autonomic disturbances. Although very common and mostly benign, prolonged or recurrent syncope may terminate into death or significant neurological sequelae.

Clinically, irrespective of the cause, most syncopal attacks are characterized by—(a) sudden onset, (b) transient dizziness or loss of sensorium for not more than 1–5 minutes, (c) spontaneous recovery in most cases, and (d) tendency for recurrence.

Etiologically, syncopal attacks may be divided as:

- *Simple or vasovagal syncope*, more common in adolescent females, precipitated by pain, fear, heat or sudden change in posture.
- *Cardiogenic syncope*, due to underlying coronary artery disease, arrhythmia (long QT syndrome) or left ventricular outflow obstruction, e.g. aortic stenosis, often precipitated by exercise or stress.
- *Cough syncope*, e.g. in asthma, pertussis, etc. due to sudden rise in intrathoracic pressure with consequent drop in systemic venous return > cardiac output > cerebral blood flow.
- *Hypoglycemic syncope*, usually seen after prolonged fasting or in insulin-dependent diabetics, with profuse sweating, cloudy sensorium. It is relieved quickly after eating.
- *Neuro-psychiatric syncope* may be seen in migraine, anxiety disorders, hysteria or breath-holding spells.

While transient EEG changes are common and clinical presentation often mimics absence seizures, syncope is not a seizure disorder.

Diagnostic evaluation of these cases aims to distinguish rare cases of organic syncope from simple vasovagal episodes. *Tilt-table test* and c*arotid massage* are two simple and reliable tests to identify simple syncope, while selected recurrent cases need 24-hour Holter monitoring, EEG studies and behavioral assessment, to exclude other causes.

Treatment depends on the cause. Although no treatment is necessary for single attacks except counseling, recurrent vaso-vagal syncope may be treated with β-blockers.

Paroxysmal non-epileptic events (pseudoseizures or psychogenic seizures) are common in adolescents, specially females or those with neurotic personality. Past history of true epilepsy may be present in some cases.

Pseudoseizure is primarily a diagnosis of exclusion, that should be suspected in cases with—(a) bizarre motor movements with unusual postures, (b) absence of cyanosis, tongue-bite, urine/stool incontinence during the episode, (c) ability to enact the seizure on request, (d) normal EEG after seizure. *Serum prolactin levels are significantly increased after true seizures but not in pseudoseizures.* Psychiatric consultation is necessary in these cases.

Behavioral disorders, e.g. breath-holding spells (Ch 4.6.1) and night terrors (Ch 4.5.) may also be confused by epilepsy.

Benign paroxysmal vertigo is mainly seen in toddlers (rare >3 years) with paroxsymal attacks of ataxia, nystagmus and vomiting with pale, frightened appearance. Each attack may last from few minutes to days with variable frequency and severity. Neurological examination is normal except an *abnormal caloric test* during attack. These children are susceptible for motion sickness and migraine in late life. Severe or frequent attacks may be treated with PO diphenhydramine (5 mg/kg/d) or Flunarizine.

Apart from seizures, these cases should also be differentiated from other causes of vertigo in childhood,

e.g. (a) acute labyrinthitis, (b) *meniere* syndrome, (c) motion sickness, (d) migraine, (e) cerebrovascular episodes, and (f) cerebello-pontine angle tumors.

Benign neonatal sleep myoclonus presents with a burst of myoclonic or clonic movements *only* during sleep in the first week of life, which is typically aborted as soon as the baby awakens. Episodes may last for few weeks to months before disappearance and no treatment is required except reassurance.

Cataplexy manifests as sudden and transient (a few seconds) loss of muscle tone with fall, precipitated by laughter, stress or frightening experience (d/d atonic seizures). Many neurostimulant and neurodepressant drugs have been used in these cases.

Narcolepsy, an uncommon paroxysmal disorder before adolescence, denotes *paroxysmal attacks of irrepressible sleep attacks during day time*, from which the patient is easily arousable (d/d true absence seizures). EEG reveals intermittent attacks of REM sleep. *Modafinil acetamide* (PO 200 mg OD) is drug of choice in confirmed cases.

Shuddering attacks are seen in 6 months-6 years age group as multiple clusters of shivering movements with intervening asymptomatic periods. Many of these cases may develop benign tremors in later age.

Drug dyskinesia, usually after antiemetics or tranquilizers, presents with sudden bizarre dystonic movements and oculogyric crisis, with normal consciousness, speech may be slurred during the attack. These movements are rarely recurrent and history of suspected drug ingestion helps in diagnosis. Although most attacks abort gradually in next 6–12 hours, *Diphenhydramine hydrochloride* may be used in cases with severe painful dystonia.

18.7 CEREBROVASCULAR STROKES

Cerebrovascular stroke is an important cause of acute neurological injury in children with considerable risk of long-term morbidity and sometimes, mortality. Most of these cases present with acute or sub-acute onset of motor deficit, e.g. hemiplegia with or without involvement of speech, vision and other neurological elements.

According to the pathogenesis, strokes may be broadly divided into three groups—*(a) Arterial ischemic strokes, (b) Cerebral sinovenous Thrombosis, and (c) Hemorrhagic strokes* **(Table 18.21)**.

Arterial ischemic strokes (AIS) are caused by thromboembolic events involving internal carotid, vertebrobasilar or any other major artery forming circle of Willis **(Fig. 18.2)**. Middle cerebral artery is most commonly affected due to being in direct anatomical continuation of internal carotid artery.

Etiologically, Vascular malformations, intracranial infections, severe dehydration and systemic diseases

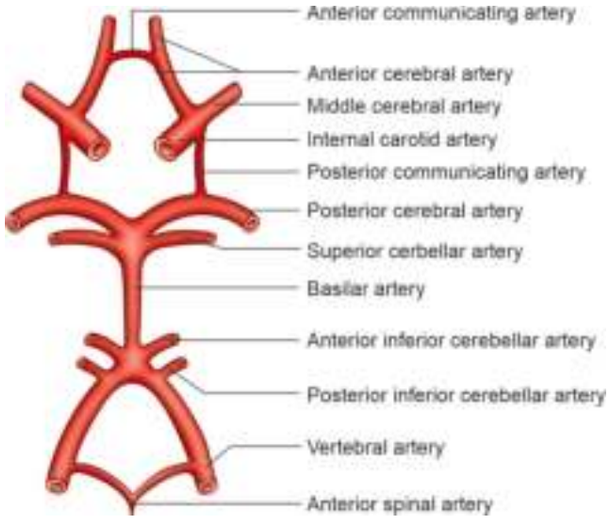

Fig. 18.2: Circle of Willis.

predisposing thromboembolic complications are predominantly identified causes of AIS in young children, though ~50% cases are idiopathic in origin **(Table 18.21)**.

Transient, focal and non-progressive *childhood primary angiitis of the central nervous system* (cPACNS) is an important emerging cause of AIS in healthy school children, discussed later. Diffuse and progressive vasculitis is rare and can represent progressive cPACNS *or* secondary vasculitis in intracranial infections *or* collagen disorders.

Cardioembolic stroke account for ~25% of AIS in children, often associated with cyanotic heart diseases, infective endocarditis or invasive cardiac procedures/surgery.

Moyamoya disease is an idiopathic, chronic cerebrovasculopathy, characterized by progressive stenosis of the distal internal carotid artery and its main branches along with development of compensatory collateral vessels at the base of the brain giving a *puff of smoke appearance* on angiography. Similar angiographic features, when seen in other identifiable conditions, e.g. sickle cell disease are termed as *Moyamoya syndrome*.

Prothrombotic or hypercoagulable states may be inherited, e.g. protein C or S deficiency, factor V leiden thrombophilia or acquired, e.g. in severe dehydration, nephrotic syndrome or DIC.

Large vessels, e.g. internal carotids or vertebral arteries are usually involved in traumatic or infective lesions of neck, spine and head. Medium-sized vessels are predominantly involved in embolic episodes from extracranial sources, e.g. sickle cell disease, infective endocarditis, etc. Thrombosis of small and distal vessels is usually caused by *end-arteritis obliterans* in meningitis, sickle cell anemia and collagen disorders.

Clinically, AIS usually present with *acute catastrophic onset* of motor deficit, specially hemiplegia with or

TABLE 18.21: Causes of cerebrovascular strokes

Arterial Ischemic Strokes (Thrombo-embolic)

- **Idiopathic:** Childhood primary angiitis of CNS
- **AV malformations:** Moyamoya disease, Sturge-Weber syndrome
- **Infections:**
  - *Intracranial:* Meningitis, encephalitis, brain abscess
  - *Extracranial:* Sepsis, head and neck infections
- **Hypovolemia:** Severe dehydration, diabetic ketoacidosis
- **Hematologic:** Sickle cell disease, polycythemia, prothrombotic states
- **Cardiac:** Cyanotic heart disease, arrhythmia, infective endocarditis
- **Vasculitis:** Aortoarteritis, collagen disorders
- **Metabolic:** Homocysteinuria, mitochondrial encephalopathies
- **Traumatic:** Cerebral arterial dissection, crush injuries (fat embolism)
- **Neoplasms:** Leukemia, brain tumors
- **Others:** Migraine, fibromuscular dysplasia

Cerebral Sinovenous Thrombosis

- **Hypercoagulable states:**
  - *Inherited:* Factor V Leiden, protein C or S deficiency
  - *Acquired:* Dehydration, DIC, nephrotic syndrome
- **Infections:**
  - *Intracranial:* Meningitis, brain abscess
  - *Extracranial:* Sepsis, sinusitis, mastoiditis
- **Traumatic:** Head injury, neurosurgery, jugular lines
- **Developmental** Venous malformations
- **Systemic:** Leukemia, SLE, homocystinuria

Hemorrhagic States

- **Trauma:** Head and neck injuries
- **AV malformation:** Moyamoya disease, aneurysms
- **Hemorrhagic disorders:** Hemophilia, DIC, anticoagulant therapy
- **Others:** Hypertension, brain tumors

without sensorium, speech and vision involvement. Cranial nerve involvement is common.

Diagnosis: Neuroimaging is an urgency in AIS. While CT scan may demonstrate mature AIS and exclude hemorrhage, MRI is preferable to identify early and small infarcts. MR angiography is required to assess the site and extent of vascular occlusion as well as feasibility for vascular interventions.

All cases also need thorough cardiac, prothrombotic and infection work-up to identify the etiology and risk of recurrence.

Management involves early anti-thrombotic therapy to prevent re-infarction with *anticoagulants*, e.g. unfractionated or low-molecular weight heparin (SC 0.5–1 mg/kg q12hr to target INR of 2–3) followed by low-dose *anti-platelet agents*, e.g. aspirin, for 4–6 months. Duration of therapy depends on the risk of recurrence. *Emergency thrombolysis with tissue plasminogen activator (tPA), widely used in adults, is generally not recommended for children.*

Supportive measures to prevent progressive ischemic brain injury include management of seizures, ventilation and cerebral perfusion along with maintenance of normothermia, normotension, normovolemia, and normoglycemia. Cerebral edema may be life-threatening and need emergency surgical decompression.

Disease-specific treatments include blood transfusion in sickle cell disease, immunosuppression in vasculitis and revascularization surgery in moyamoya disease. Appropriate physiotherapy and occupational therapy is necessary for residual deficits. Secondary prevention may need long-term anti-platelet therapy or anticoagulation, depending on the cause.

Outcome includes risk of immediate mortality in 6–10%, recurrent strokes in 10–50% and neurological sequelae in 60–70%.

Cerebral sinovenous thrombosis (CSVT) is more common in children than in adults. Normal cerebral venous drainage involves superficial (cortical veins, superior sagittal sinus) and deep (internal cerebral veins, straight sinus) systems that converge at the torcula to exit via the paired transverse and sigmoid sinuses and jugular veins. Thrombotic occlusion of these structures may lead to venous infarcts or hemorrhagic strokes.

Etiologically, CSVT is usually caused by severe dehydration, prothrombotic states and infections **(Table 18.20)**. *Sagittal sinus thrombosis* is usually a complication of bacterial meningitis while *Cavernous sinus thrombosis* generally follows intracranial extension of paranasal or retroorbital infections. Lateral sinus thrombosis may develop as a complication of mastoiditis.

Clinically, onset of CSVT is relatively more insidious than AIS with raised intracranial pressure as predominant presentation. Most cases present with progressive headache, vomiting, diplopia and papilledema. Seizures and focal neurological deficits are less common. Proptosis is common in cavernous sinus thrombosis.

Diagnosis requires CT or MR venography to demonstrate filling defects in the cerebral venous system, though contrast CT or MRI may be informative.

Management revolves around anticoagulant therapy with unfractionated or low-molecular weight heparin followed by oral anticoagulants, e.g. Warfarin for 3–6 months, till reimaging confirms recanalization. Children with persistent risk factors may require long-term anticoagulant prophylaxis.

Supportive measures include management of infection, seizures and raised intracranial pressure along with maintenance of normothermia, normotension, normovolemia, and normoglycemia. Appropriate physiotherapy and occupational therapy is necessary for residual deficits. Optic neuropathy secondary to increased intracranial pressure is common and regular fundoscopy is required to detect and prevent visual loss.

Hemorrhagic strokes (HS) are relatively uncommon in children than in adults, usually seen in cases with

intracranial arteriovenous malformations, accidental or non-accidental (battered baby) head injuries and bleeding disorders. Bleeding may occur within (intraparenchymal, intraventricular) or outside (subarachnoid, subdural, epidural) the brain.

Clinical presentation varies with size and location of bleeding. Unlike AIS, HS usually evolve slowly with progressive headache, altered sensorium and nuchal rigidity, followed by seizures and focal neurologic deficits. However, some HS can be rapidly fatal. In bleeds due to vascular malformations, pulsatile tinnitus, cranial bruit and high-output heart failure may be present.

Diagnosis rests on neuroimaging. While CT is highly sensitive for acute HS, MRI may be more useful to detect small and chronic bleeds. Conventional or CT/MRI angiography is required to exclude vascular anomalies. Lumbar puncture helps to exclude subarachnoid hemorrhage.

Management involves emergency neurosurgical decompression for large or rapidly expanding hematoma along with supportive measures as discussed earlier for ischemic infarcts. Reversal of anticoagulant therapy (e.g. vitamin K, fresh-frozen plasma) may be required. Definitive management of vascular malformation may require surgical or endovascular interventions.

Outcome depends on size, location, and etiology of bleeding. Immediate mortality is higher in HS than in AIS or CSVT. Recurrence risk is high in cases with untreated vascular malformations **(Table 18.21)**.

Childhood Primary Angiitis of Central Nervous Systems (cPACNS)

cPACNS, also termed as *Focal cerebral arteriopathy*, is an idiopathic cerebrovasculopathy characterized by-(a) newly acquired neurologic deficits and/or psychiatric symptoms, *plus* (b) angiographic or histologic evidence of vasculitis with luminal stenosis, and (c) *in absence of* a systemic, identifiable cause.

cPACNS may involve large/medium vessels or small vessels. While large/medium vessel disease may be progressive or non-progressive, small vessel disease is usually progressive and easily missed on angiography.

Clinically, most cases present with unexplained AIS or refractory status epilepticus, though presentation is extremely wide. Cognitive dysfunction, behavior changes and loss of social/emotional is common. cPACNS may also present with newly acquired migraine without family history.

Diagnosis is confirmed on neuroimaging, i.e. inflammatory or ischemic parenchymal lesions on MRI and evidence of vessel stenosis on angiography. Brain biopsy is required only in small vessel disease where angiography may be normal.

Treatment involves antithrombotic therapy with low-molecular-weight heparin or long-term anti-platelet agents, e.g. aspirin for 12 months. Re-imaging is advised after 3 months to monitor progression of disease. However, anti-platelet agent should continue for 18–24 months to prevent recurrent ischemic events. Role of steroids is controversial in non-progressive cases. However, some studies have shown reduced recurrence risk when steroids are used in combination with aspirin.

Long-term steroids or second-line immunosuppressive agents, e.g. cyclophosphamide or mycophenolate may be required in cases of progressive or small/medium vessel cPACNS. Outcome is relatively better in large vessel disease than in those with small vessel disease. Children presenting with status epilepticus and Small vessel disease have the poorest outcome.

18.8 HEMIPLEGIA

Hemiplegia, i.e. unilateral weakness, may be acute, chronic progressive or static.

- *Acute hemiplegia of childhood* is the major cause of concern in childhood, almost always suggestive of *cerebrovascular accidents or strokes*. Severity of motor deficit is maximum at the onset of illness and recovery is usually faster than other causes.
- *Chronic progressive hemiplegia* usually indicates: (a) focal CNS infections, e.g. brain abscess, tuberculoma, (b) brain tumors, and (c) neurocutaneous disorders, e.g. Sturge-Weber syndrome, and (d) early stages of white matter degenerative disorders.
- *Static hemiplegia* usually denotes hemiplegic cerebral palsy due to: (a) perinatal hypoxic-ischemic insult, and (b) congenital malformations.
- *Recurrent or alternating hemiplegia* is seen in: (a) migraine, (b) hypercoagulable states, e.g. protein C or S deficiency, (c) vascular malformations, e.g. Moya-Moya disease, and (d) mitochondrial encephalopathies, e.g. *MELAS* (***M***yoclonic ***E***pilepsy, ***L***actic ***A***cidosis and recurrent ***S***troke-like syndromes.
- *Todd paralysis* is transient cause of unilateral weakness after seizures, which may be recurrent but does not last for more than 24 hours.

Diagnostic approach in hemiplegia aims to—(a) localize the site of lesion, and (b) identify probable cause on the basis of clinical and laboratory findings.

A. Clinical localization of lesion is possible up to certain extent, according to type of hemiparesis and presence of clinical signs **(Table 18.22)**. Hemiplegia may be caused by any lesion from the cerebral cortex to upper few segments of spinal cord. Important localizing clues are:

- *Side of hemiplegia:* Hemiplegia is almost always contralateral to brain lesion, except in rare lower medullary lesions.
- *Extent and severity of motor deficit:* Internal capsule is the commonest site of lesion in dense hemiplegia,

TABLE 18.22: Clinical localization of lesions	
Cortical	*Non-dense* contralateral hemiparesis Seizures Altered sensorium Motor aphasia (dominant side lesion)
C. radiata	*As above*, but without seizures
Int. capsule	Dense contralateral hemiplagia Contralateral sensory loss Supranuclear facial paresis
Midbrain	Contralateral hemiplagia + III/IV nerve palsy
Pons	Contralateral hemiplagia + Ipsilateral VII/VIII
Medulla	Contralateral hemiplagia + Ipsilateral bulbar palsy
Spinal cord	Ipsilateral hemiplagia, no cranial nerve palsies

while cortical and sub-cortical lesions usually produce weakness limited in severity and scattered in extent.

- *Side and type of facial palsy:* Facial palsy is also contralateral and supranuclear in lesions at *or* above the level of upper pons. Ipsilateral infranuclear facial palsy, (i.e. contralateral to hemiplegia) indicates lesions at *or* below the lower pons.

B. Etiological identification of lesion is facilitated by:

- *Onset and progress of lesion*: Thromboembolic lesions generally present with sudden catastrophic onset over a few minutes and recovery starts within few days in most cases. On the other hand, hemorrhagic lesions develop more gradually and recovery is often unsatisfactory.
- *History* of head injury, diarrhea/vomiting, fever and systemic disorders, e.g. heart disease, bleeding disorders, sickle cell disease or hypercoagulable states.
- *History of similar attacks* in past (*see* causes of recurrent or alternating hemiplegia)
- Clinical examination suggestive of neurocutaneous markers, extracranial septic focus, signs of dehydration or systemic diseases.

C. Laboratory Investigations include:

- *Neuroimaging* with CT scan/MRI. Four-vessel angiography or MR angiography is necessary in suspected cases of cerbrovascular malformations.
- *Relevant investigations* to identify or exclude:
  - *Hematological causes:* Sickling test, coagulation profile (prothrombin time, protein C and S levels, antithrombin), platelet count, etc.
  - *CNS infections:* CSF examination (should be avoided in suspected bleeding disorders).
  - *Cardiac causes:* ECG and echocardiography
  - *Connective tissue disorders:* ESR, antinuclear antibodies, etc.
  - Metabolic disorders — urine analysis, lactates, homocysteine levels, blood gas analysis for acidosis and enzyme studies.

Despite extensive investigations, underlying cause in acute hemiplegia of childhood remains unidentified in 60–70% cases.

Management of hemiplegia is largely supportive, including:

- *General supportive measures*, e.g. (i) nursing care (care of back, bowel and bladder), (ii) nutritional support, (iii) control of associated problems, e.g. seizures, raised ICP, etc.
- *Physiotherapy*, speech therapy and rehabilitation, should be started as early as possible.
- *Specific therapy* is of limited value in established case. However anti-thrombotic and anti-platelet therapy is required in cases of arterial ischemic strokes or cerebral sinovenous thrombosis, as discussed in Ch 18.7. Surgical evacuation of clot is indicated in cases of large hematoma.
- *Preventive therapy* depends on suspected cause. Salicylates, vasodilators and platelet inhibitors have been used to prevent recurrence of thromboembolic episodes.

18.9 MOVEMENT DISORDERS

The term *Movement disorders refers to many* transient or persistent and pathological or psychological disorders, characterized by abnormal movements and/or posturing of all or parts of body (*excluding seizures*). These disorders are generally *cerebellar* or *extrapyramidal* in origin and usually aggravate by activity/stress and disappear in sleep.

Movement disorders are classified as *hyperkinetic* or *hypokinetic*. Hyperkinetic disorders include ataxia, chorea, athetosis, tremors, myoclonus and tics. Hypokinetic disorders with paucity of movements are rare in children and include juvenile parkinsonism. Many movement disorders may co-exist in the same patient.

Ataxia denotes '*inability to sustain a posture or perform smooth and accurate movements due to lack of coordination between different groups of muscles*'.

Ataxia may be (a) *truncal* (abnormality in maintaining the erect posture), (b) *appendicular* affecting the limbs (difficulty in performance of certain coordinated acts), or (c) mixed.

Etiologically, Fine control of posture and movements requires normal positional sensory inputs from posterior spinal columns and vestibular system as well as normal cerebellar functions. Accordingly, ataxia may be cerebellar, sensory or vestibular in origin **(Table 18.23)**. Isolated truncal ataxia is common in mid-line cerebellar lesions while isolated appendicular ataxia is seen in lesions of cerebellar hemispheres.

In children, Acute cerebellar ataxia following viral infections and drugs, e.g. anticonvulsants is most common.

TABLE 18.23: Causes of ataxia in children

A. Cerebellar ataxia
- Acute cerebellar ataxia (Post-infectious cerebellitis)
- Ataxic cerebral palsy
- *Infections:* Encephalitis, cerebellar abscess
- Congenital cerebellar malformations, hydrocephalus
- *Toxic:* Alcohol, anticonvulsants*, pesticides
- *ICSOL:* Tumors, tuberculoma, neurocysticercosis
- *Hereditary:* Ataxia telangiectasia, Friedreich's ataxia
- *Metabolic:*
  - Hypoglycemia, hyperammonemia
  - *IEMs:* Wilson disease, abetalipoproteinemia
- *Others:* Post-ictal, post-traumatic, basilar migraine

B. Sensory ataxia
- Polyneuropathies
- Intramedullary spinal tumors
- Subacute combined degeneration of spinal cord

C. Vestibular Ataxia
- Acute labyrinthitis
- Middle ear disorders,
- Benign paroxysmal vertigo

ICSOL: Intracranial space occupying lesion; **IEM:** Inborn errors of metabolism
*e.g. Phenytoin, Carbamazepine.

Clinically, Ataxia may be acute or persistent and important clinical signs include:
- Abnormal gait (*Wide-base gait*) and inability to walk in a straight line (*Tandem walking*). While walking or standing, child tends to sway towards the side of cerebellar lesion. Children with sensory ataxia usually have *stamping gait*, due to difficulty in assessing the distance from ground.
- Impaired coordination, as assessed by *Finger-nose test* or *Heel-to-shin test*, even with open eyes.
- *Romberg sign*, i.e. failure to stand erect steadily with outstretched hands, helps to distinguish cerebellar from sensory ataxia. Inability to maintain normal posture even with open eyes indicates cerebellar ataxia.
- O*ther cerebellar signs*, e.g. dysdiadochokinesia, nystagmus, dysarthria, pendular jerks and hypotonia indicate cerebellar ataxia.
- Vestibular ataxia is associated with vertigo and nystagmus.

Evaluation: Most cases of ataxia are viral and self-limiting. However, neuroimaging studies are indicated in cases with—(a) progressive or persistent ataxia >1 week and, (b) presence of other neurological signs. MRI is preferable in ataxic children, as infratentorial cerebellar lesions are not well visualized on CT scan.

Management include treatment of primary cause, though most cases in children are due to self-limiting post-viral acute cerebellar ataxia.

Some common causes of ataxia are as follows:

Acute cerebellar ataxia following viral infections, e.g. varicella, coxsackievirus or echovirus infection is the *commonest* cause of ataxia in children between 1–5 years of age. Ataxia may develop within a few hours of viral illness and usually self-limiting with complete recovery within 3–7 days. No specific treatment is required.

Recurrent ataxia with intervening normal period is seen in: (a) basilar artery migraine (Benign paroxysmal vertigo, Ch 18.6.5), (b) epileptic disorders (during post-ictal state), and (c) inborn errors of metabolism, e.g. hypoglycemia, hyperammonemia and ion channel mutations, e.g. KCNA1.

Hysterical ataxia is a conversion reaction more common in adolescent girls to cope with a stress or for some secondary gain, though many events are involuntary. Unlike organic ataxia, these children usually do not injure themselves and diagnosis depends on discrete observation.

Dystonia refers to *slow, intermittent and sustained twisting motion of the trunks and limbs with development of abnormal postures*, due to sustained contraction of agonists and antagonists group of muscles. Dystonia may be painful and aggravate during stress or voluntary activity.

Etiologically, Dystonia may be isolated or secondary.

Isolated dystonia without other motor components is almost always genetic in origin, commonest being DYT-TOR1 dystonia with onset in late childhood or adolescence.

Secondary or combined dystonia with other motor components may be due to: (a) cerebral palsy, (b) juvenile parkinsonism, (c) drugs, e.g. phenytoin, phenothiazines, metoclopramide, (d) metabolic disorders, e.g. Wilson disease, and (e) neurotransmitter disorders.

Clinically, Acute-onset dystonia is usually secondary to drugs, while dystonia due to genetic causes is usually paroxysmal in nature with recurrent history and normal intervening period.

Status dystonicus is a life-threatening condition, with frequent or continuous generalized dystonic spasms, common in cerebral palsy or neurodegenerative disorders, often precipitated by fever or other stressors.

Diagnosis needs assessment for age of onset, distribution (focal/generalized), progression (static/progressive) and presence of other neurological and systemic abnormalities, followed by ophthalmic examination (KF ring, retinitis pigmentosa) and MRI (essentially normal in primary DYT dystonia) in all cases and metabolic screening or genetic studies in selected cases.

Management include treatment of primary cause, if identified, along with symptomatic therapy with therapeutic trial of levodopa in all dystonic children. However, the response is variable and often unsatisfactory. Neurosurgical procedures, e.g. deep brain stimulation may help in refractory cases.

Status dystonicus needs careful use of sedatives including chloral hydrate (PO 30–100 mg/kg/dose 3–4 hourly) with/without clonidine (3–5 µg/kg/dose

6–8 hrly). Continuous midazolam infusion may also be effective. Dystonia-specific drugs, e.g. Trihexyphenidyl (Pacitane) or Tetrabenazine, etc. may be required on long-term basis.

Chorea is defined as involuntary *quick, random, jerky movements of skeletal muscles,* mainly at the proximal joints, e.g. shoulder, etc. Hemichorea is the unilateral variant. *Motor impersistence,* i.e. inability to maintain sustained posture makes the child appears fidgety or hyperactive. Important clinical signs of chorea include: (a) inability to keep the arms when extended above the head with palms facing inward, (b) inability to keep tongue protruded, i.e. *Lizard tongue, darting tongue or tongue in jack box appearance,* and (c) inability to sustain the grip over examiner's finger, i.e. *milkmaid's grip* (Ch 17.6).

Etiologically, Important causes of chorea include: (a) Sydenham or rheumatic chorea, (b) Huntington or familial chorea, (c) drugs, e.g. phenytoin, amitriptyline, etc., (d) Wilson disease, and (e) others, e.g. SLE, hyperthyroidism, hypoparathyroidism. Among these, rheumatic chorea is the commonest cause of chorea in children (Ch 17.6), followed by Wilson disease.

Choreiform movements may also be seen during recovery phase of tubercular meningitis or encephalitis, along with other abnormal movements, e.g. athetosis.

Management: Antipsychotic agents like olanzapine or risperidone may be useful for symptomatic control of acute onset chorea with alternatives including Tetrabenazine and anti-epileptics like valproic acid or carbamazepine.

Rheumatic (Sydenham) chorea is the commonest cause of chorea in Indian children, discussed in Ch 17.6.

Benign hereditary chorea is a rare autosomal dominant disorder with onset at 2–5 years of age and improvement in adulthood. Intelligence is normal Huntington chorea (autosomal dominant) is a progressive NDD of middle-age adults with predominant basal ganglia involvement. Less that 1% cases present in childhood with progressive rigidity, dystonia, chorea, dementia and seizures. Diagnosis is clinical, though CT may show basal ganglia atrophy. Management is nonspecific and most cases die within 10–15 years.

Ballismus and hemiballismus, i.e. *frequent, violent, rapid, flinging movements of proximal joints* of one or both arms, usually indicates vascular or neoplastic lesions near the sub-thalamic nuclei. It is uncommon in children.

Athetosis presents as *irregular, often continuous, slow writhing movements of the extremities,* mainly in distal parts, e.g. alternate pronation and supination of wrists. Common causes include: (a) cerebral palsy, (b) cerebral hypoxia, (c) meningitis, (d) hypothermia and (e) drugs, e.g. phenothiazines.

Stereotypic movement disorders: Stereotypies are repetitive, non-functional, patterned movements and/or vocalizations, which can be suppressed by distraction. Simple stereotypies like leg-shaking, body-rocking etc are common in normal children, which disappear with time. Complex stereotypies like hand-flapping, oro-facial movement and eye-poking, which interfere with functions or may be self-injurious, are abnormal.

Complex stereotypies are usually associated with Rett syndrome, autism, intellectual disability and in children with vision or hearing impairment. Treatment of primary disease along with behavioral therapy may be useful in these cases.

Tics are sudden, brief, purposeless, stereotyped movements, which are exacerbated in stress and disappear during sleep. While habit tics are common in most children, persistent and debilitating tics suggest possibility of *Tourette syndrome* (Ch 5.5.4).

Tremors are *prolonged or continuous involuntary rhythmic movements of usually distal parts,* e.g. *fingers*, which may be coarse or fine. Tremors are best demonstrated on outstretched hands and usually tend to diminish during sleep. Jitteriness in newborns is also a type of tremor. Tremors are also classified as resting tremors or action tremors.

Transient tremors in older children are commonly seen during salbutamol therapy. Other causes of tremors include: (a) essential or idiopathic tremors, (b) *infantile tremor syndrome*, (c) drugs, e.g. salbutamol, aminophylline or substance abuse, (d) metabolic disorders, e.g. acute hepatic failure, Wilson disease, hypoglycemia, and (e) others, e.g. thyrotoxicosis or neuroblastoma.

Infantile Tremor Syndrome

Infantile tremor syndrome (ITS) is characterized by a clinical tetrad of—(a) *tremors, (b) developmental regression, (c) moderate anemia of usually megaloblastic type, and (d) hyperpigmentation of skin*. ITS is largely confined to Indian subcontinent and the incidence has declined in recent years.

Epidemiology: ITS is typically seen in children between 6 months to 3 years, more common in: (a) boys, (b) low socioeconomic status, (c) fullterm birth, (d) prolonged breastfeeding, (e) second or subsequent birth order, and (f) summer season (April to July).

Etiopathogenesis is unexplained, though various suggestions include: (a) nutritional recovery syndrome similar to that in malnutrition with relative GABA deficiency, (b) vitamin B_{12} deficiency, (c) trace-element deficiency, e.g. hypomagnesemia or hypozincemia, (d) low-grade meningoencephalitis, (e) transient metabolic defect in tyrosine metabolism, and (f) toxic insult to growing brain due to some unidentified toxin in breast milk.

Clinically, ITS may be divided into three stages:

a. ***Pre-tremor phase***, characterized by developmental regression in a previously normal child, lasting from few days to many weeks.

b. ***Tremor phase***, often preceded by stress factors, e.g. respiratory infection or diarrhea, is characterized by:
   - Neurological signs including: (a) abrupt onset of generalized coarse tremors, most prominent in hands, head and tongue, which intensify during activity and disappear on sleep, (b) generalized hypotonia, (c) vacant and expressionless face, (d) side to side tossing movements of head, and (e) typical tremulous cry like *bleating of a goat*
   - Mild to moderate anemia, often *megaloblastic* or dimorphic type.
   - *Dark-brown hyperpigmentation* of skin, mainly on the dorsum of hands/feet, groin, medial side of thigh and axilla. Hairs are often light-brown, sparse and lusterless, as seen in kwashiorkor.

     Tremor phase is *self-limiting*, with abrupt cessation of tremors after few weeks (usually 2–3 week).

c. ***Post-tremor phase*** denotes convalescence with regaining of milestones and disappearance of skin signs in next few weeks. Although long-term cognitive dysfunctions have been reported, mortality is almost nil due to ITS.

Diagnosis is largely clinical, supported by presence of megaloblastic/dimorphic anemia and normal CSF.

Transient, non-specific EEG abnormalities are common. CT/MRI may reveal ventricular dilatation in some cases.

Management is empirical, including-(a) correction of megaloblastic anemia with Vitamin B_{12} and folic acid supplements, (b) mild sedation with phenobarbitone or chlorpromazine in severe tremors, and (c) nutritional supplementation. Unexplained improvement has been claimed with oral propranolol or emetine therapy.

18.10 CONGENITAL CNS MALFORMATIONS

Congenital CNS malformations account for ~5–10% of all major malformations in live births.

Embryology: Development of CNS may be broadly divided into three steps **(Fig. 18.3)**, as follows:

a. ***Formation of neural tube:*** CNS develops from the *primitive ectoderm,* which forms a neural plate during 3rd–4th weeks of gestation, overlying the notocord. Central indentation of this plate leads to formation of *neural groove* flanked by ridges, i.e. neural folds, which later fuse together in midline to form the neural tube.

b. ***Segmentation of neural tube:*** Cephalic portion of neural tube develops three saccular segments to form ventricular system and aqueduct, while walls of these dilatations develop into *prosencephalon* (cerebral hemispheres), *mesencephalon* (pons and cerebellum) and *Rhombencephalon* (medulla). Caudal portion develops into spinal cord. Peripheral nerves, spinal/autonomic ganglions, leptomeninges and lower cranial nerve ganglions develop from neural crest.

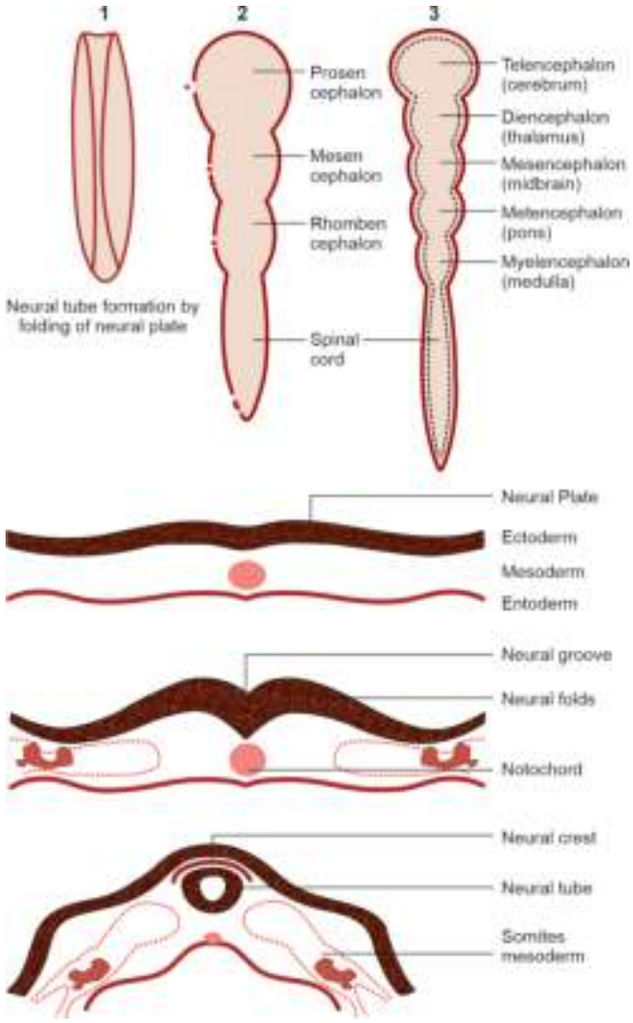

Fig. 18.3: Development of CNS.

c. ***Migration of neuronal cells:*** Functional maturation of CNS involves development of primitive neuroepithelial cells in periventricular region, which then migrate outwards towards the surface of cortical hemispheres. Increasing cellular activity leads to development of sulci and gyri on cerebral surface, to increase the surface area of brain.

CNS malformations may develop either due to defective formation *or* segmentation of the neural tube or due to abnormalities in migration and maturation of neuronal cells **(Table 18.24)**, some of whom are discussed here.

18.10.1 NEURAL TUBE DEFECTS

Neural tube defects (NTDs) is a collective term for broad spectrum of developmental defects, due to defective

TABLE 18.24: Developmental CNS malformations

- *Defective formation of neural tube (Neural tube defects)*
  Spina bifida occulta
  Meningocele/Myelomeningocele
  Encephalocele
  Anencephaly
- *Defective segmentation of neural tube*
  Holoprosencephaly
  Porencephaly
  Agenesis of corpus callosum
- *Disorders of neural migration or sulcation*
  Lissencephaly
  Schizencephaly
- *Disorders of neurological growth*
  Microcephaly
  Hydrocephalus
  Craniosynostosis

fusion of neural tube, ranging from asymptomatic spina bifida occulta to most severe anencephaly and encephalocele.

Overall incidence of NTDs in India is estimated to be ~ 1.5/1000 live births, more common in north India and Punjabi population (4–8/1000).

Etiology: While some NTDs are part of chromosomal disorders, e.g. Trisomy 13 (Patau syndrome), isolated NTDs are multifactorial in origin. Dietary folates and folic acid also have an important role in causation of NTDs.

Important *maternal risk factors* for NTDs include: (a) folic acid deficiency, (b) severe malnutrition, (c) alcohol abuse, (d) radiation exposure, (e) diabetes mellitus and (f) anticonvulsant-exposure, e.g. valproate or carbamazepine.

Clinical spectrum varies according to the type of defect, as follows:

a. **Meningomyelocele** is the commonest identified neural tube defect (NTDs), characterized by protusion of meningies and neural tissue remnants through a midline vertebral column defect (dysraphism), with or without secondary neurological damage. Clinical features include:
   - *Posterior midline cystic (translucent) mass*, usually in lumbosacral region, covered with thin layer of partially epithelialized tissue **(Fig. 18.4)**.
   - *Secondary neurological damage* depending on location of the lesion, e.g. paraplegia with/without sensory damage and bladder/bowel involvement
   - *Associated abnormalities*, e.g. (a) Arnold-Chiari malformation with hydrocephalus, (b) genitourinary tract abnormalities, and (c) skeletal defects, e.g. club feet and congenital dislocation of hip.

b. **Meningocele** is the milder variant, in which herniated sac contains only meninges and no neural tissue. However, associated abnormalities, e.g. syringomyelia, diastematomyelia, tethered cord syndrome and hydrocephalus are not uncommon and should be excluded by MRI, before surgery.

Fig. 18.4: Meningomyelocele.

c. **Encephalocele** is the cranial variant of the meningocele, characterized by herniation of a meningial sac with/without brain matter, from occipital or frontal region. Associated malformations include hydrocephalus, Arnold-Chiari malformation, Dandy-Walker cysts, etc.

d. **Anencephaly** is the most severe NTD, characterized by a large defect in calvarium, meninges and scalp with rudimentary brain, due to failure of closure of the rostral neuropore. The primitive brain usually contains only residual brain-stem, without cerebrum, cerebellum and other structures. *Polyhydramnios* is common. Child usually succumbs in few days.

e. **Spina bifida occulta** is the commonest, though frequently missed NTD, characterized by midline defect in vertebral bodies covered with skin *without* protrusion of spinal contents, usually at L_5-S_1. Presence of a tuft of hair, dermal sinus, discoloration or lipoma over spine indicates possibility of underlying spina bifida occulta. Presence of dermal sinus with spina bifida occulta may lead to recurrent meningitis.

Diagnosis of NTDs is clinically obvious, except in spina bifida occulta, but further investigations are essential to exclude other problems, e.g. (a) *Neuroimaging* of entire spine and brain to exclude hydrocephalus, and (b) *Renal USG* to exclude congenital anomalies and bladder dysfunction, which are common in these cases.

Neuroimaging (MRI) is indicated even in spina bifida occulta to exclude cord defects, e.g. syringomyelia, diastematomyelia and tethered cord syndrome.

Prenatal diagnosis of NTDs is possible by 16–18 weeks, on antenatal USG or presence of following biochemical markers:

- Elevated α-fetoprotein levels in maternal serum with 60–70% sensitivity;
- Elevated α-fetoprotein *or* acetylcholinesterase levels in amniotic fluid, with ~100% sensitivity.

Management of NTDs depends on the severity of defect, presence of secondary neurological deficits and other congenital anomalies. Immediately at birth, open defects should be covered with sterile wet gauze to prevent drying, cracking and infection of covering tissue, till surgery is arranged.

CSF examination and antibiotics are indicated in cases with ruptured membranes with CSF leak or infection, in whom surgery should be deferred till the CSF is sterile.

Early surgical repair of defect within 24–48 hours of birth along with CSF shunt (in cases with associated hydrocephalus) is indicated in selected cases of myelomeningocele. Prenatal *in utero* closure is possible at few centres, with better functional results.

However, surgery is usually futile in cases with-a) severe paraplegia, (b) gross hydrocephalus or encephalocele, (c) gross kypho-/scoliosis, (d) serious renal or other congenital anomalies ***(Lorber's criteria)***.

No intervention is required for spina bifida occulta, unless associated with other defects.

Outcome depends on presence of neurological deficit and hydrocephalus at the time of surgery. With early surgery in cases without neurological deficit, prognosis is good, though ~10–15% cases may die due to meningitis, late hydrocephalus or other malformations.

Survivors may be normal or left with—(a) paraplegia, (b) bladder/bowel incontinence, (c) seizure disorders and (d) learning disabilities or intellectual dusability.

Prevention of NTDs is a major advance in prenatal therapeutics, which involves:

- ***Genetic counselling*** regarding risk of recurrence in future pregnancy, which is ~5% (if one parent/sibling is affected) and ~10 % (if two siblings are affected).
- ***Folic acid supplements:*** All prospective mothers with history of previous NTD birth, should receive *5 mg/day of folic acid, from one months before conception till the end of first trimester*, which reduces the risk of recurrence by >50%.

  Primary prevention to all prospective mothers *irrespective* of high-risk history with lower dose of folic acid supplementation (0.4 mg/day) during this period is also recommended at present, which can reduce the risk of NTD by >70%.
- ***Prenatal diagnosis*** with USG/biochemical markers, discussed earlier, with appropriate interventions.

Some other important developmental CNS malformations are as follows:

Neural tube segmentation defects are relatively uncommon and include:

Holoprosencephaly is characterized by *incomplete separation of two cerebral hemispheres* with single ventricle, absence of falx cerebri and fused basal ganglion, due to defective cleavage of prosencephalon. Associated malformations, e.g. cyclopia (single mid-line eye), cebacephaly and premaxillary agenesis is common. Most cases die in infancy **(Fig. 18.5)**.

Porencephaly is the presence of *cysts/cavities in cerebral cortex*, which may be congenital or acquired after cerebral infarcts or hemorrhage. Congenital cysts are often CSF-filled, due to communication with subarachnoid or ventricular spaces and frequently symptomatic with focal seizures and hemiparesis **(Fig. 18.5)**.

Hydranencephaly represents an extreme form of porencephaly with near absence of cerebral hemispheres, probably related to bilateral occlusion of internal carotid arteries in early fetal life. Head size is normal at birth but enlarges rapidly with positive transillumination.

Clinically, these cases present with large head, severe developmental retardation, seizures and spastic quadriparesis. CSF shunt may prevent progression of head enlargement **(Fig. 18.5)**.

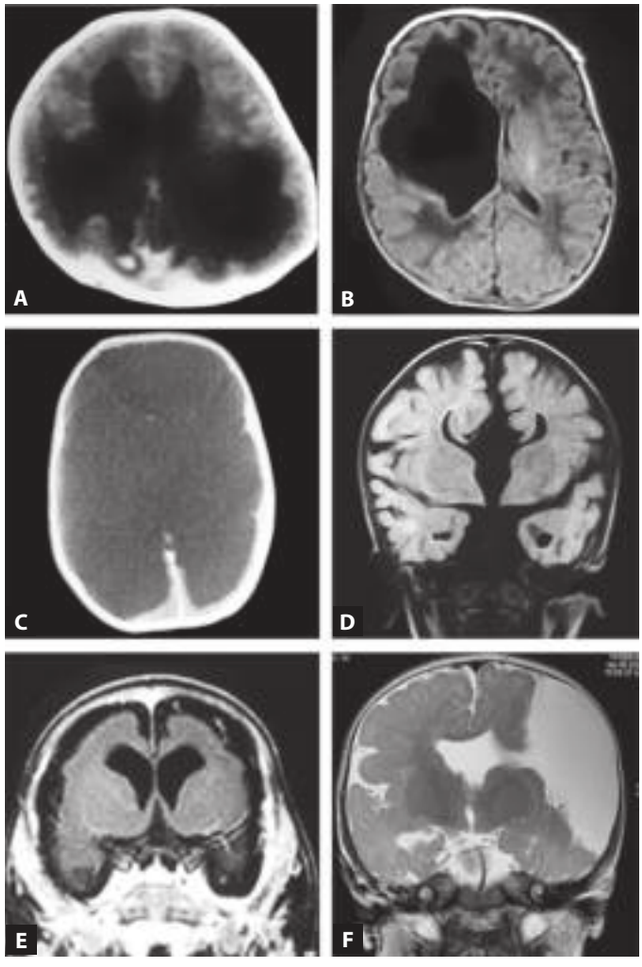

Fig. 18.5: Important development malformations of brain: (A) Holoprosencephaly; (B) Porencephaly; (C) Hydranencephaly; (D) Agenesis of corpus callosum; (E) Lissencephaly; (F) Schizencephaly

Agenesis of corpus callosum is either isolated or associated with other neurological or chromosomal disorders, e.g. *Aicardi syndrome*. These cases may be entirely asymptomatic with accidental diagnosis on CT/MRI scan *or* may present with diplegia, mental retardation and seizures **(Fig. 18.5)**.

Neuronal migration defects are easily missed on CT scan and being increasing recognized as a cause of unexplained mental retardation or refractory seizures, after advent of MRI.

Lissencephaly (agyria) is characterized by the absence of cerebral convolutions and poorly formed sylvian fissure, due to faulty migration of neuroblasts in early embryonic life. These cases present with microcephaly, severe mental retardation, seizures and failure to thrive in infancy **(Fig. 18.5)**.

Schizencephaly is characterized by presence of unilateral or bilateral clefts in cerebral hemispheres, presenting with seizures, severe mental retardation and spastic quadriparesis in bilateral lesions **(Fig. 18.5)**.

Microcephaly denotes *head circumference <3rd percentile for corresponding age and sex.*

Etiologically, it may be *primary*, associated with genetic disorders; or *secondary* due to intrauterine or postnatal insult to growing brain **(Table 18.25)**.

Clinically, microcephaly is almost always associated with mental retardation with/without seizures and features of chromosomal defects/intrauterine infections abnormal facial appearance with slanting forehead and prominent nose and ears is more common in primary microcephaly *(d/d secondary microcephaly).*

Diagnosis rests on head circumference, though etiological diagnosis requires neuroimaging, karyotyping/genetic testing and serological studies for intrauterine infections.

D/D of microcephaly includes *craniosynostosis*-a cranial vault defect with premature fusion of sutures, leading to abnormal head shapes, restricted brain growth and neuroocular abnormalities (*see* **Table 23.2)**.

Management of these cases is mainly directed towards the primary cause, though outcome is generally unsatisfactory **(Fig. 18.6)**.

TABLE 18.25: Common causes of microcephaly

Primary microcephaly
- *Genetic:* Familial (AR) or autosomal dominant
- *Chromosomal:* Trisomies, cri-du-chat syndrome

Secondary microcephaly
- *Intrauterine infections:* Rubella, CMV
- *Intrauterine radiation/drugs:* Alcohol, hydantoin
- *Birth asphyxia:* Hypoxic-ischemic encephalopathy
- *Perinatal CNS infections:* Meningitis
- Severe malnutrition (?)
- Metabolic disorders, e.g. Phenylketonuria

Fig. 18.6: Microcephaly.

18.10.2 HYDROCEPHALUS

Hydrocephalus is defined as *enlargement of the ventricular system of the brain*, due to an imbalance between production and absorption of the CSF.

CSF physiology: The normal volume of CSF is ~50 ml in infancy and ~150 ml in adults, which is in a state of dynamic equilibrium, i.e. formed and absorbed at the rate of ~20 ml/hour.

CSF is an active ultrafiltrate of plasma, mainly formed within cerebral ventricular system by the choroid plexus of lateral, third and fourth ventricle, under neurogenic and autonomic control. Adrenergic and cholinergic stimuli decrease or increase CSF production, respectively. Extrachorial CSF production (<30%) occurs in subarachnoid space and through capillary endothelium in brain parenchyma.

CSF flows forward due to a pressure gradient between intraventricular space (150 mm H_2O) and superior sagital sinus (90 mm H_2O). After formation, CSF flows from the lateral ventricle through the *foramina of Monro* into the third ventricle and then through the narrow *aqueduct of Sylvius* into the fourth ventricle, where it exits the ventricular system via paired *foramina of Luschka* and midline *foramina of Magendie*, to enter in subarachnoid cisterns. In subarachnoid space, CSF baths cerebral convexities before absorption mainly by *sub-arachnoid villi* and minimally by lymphatic channels, nerve root sheaths (*Schwann space*) and choroid plexus itself. The spinal subarachnoid space communicates with the intracranial subarachnoid space by basal cisterns **(Fig. 18.7)**.

Pathogenesis: Hydrocephalus may be caused by:
- Increased production of CSF, e.g. choroid plexus papilloma.

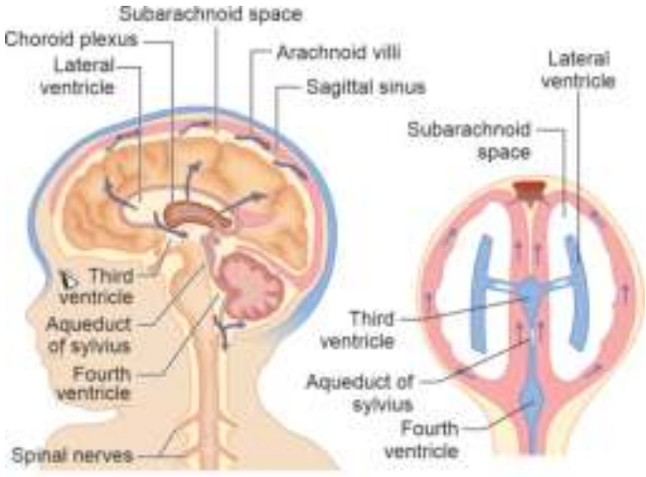

Fig. 18.7: Normal CSF flow.

- Obstruction to CSF pathway within ventricular system, i.e. *obstructive hydrocephalus.*
- Obliteration of the subarachnoid cisterns or malfunction of the arachnoid villi, i.e. *communicating hydrocephalus.*
- Dilatation of ventricles with normal or even low CSF pressure is rarely seen in neurodegenerative disorders or cortical atrophy (*low-pressure hydrocephalus).*

Etiology: Hydrocephalus may be congenital or acquired **(Table 18.26)**. Some common causes are as follows:

Congenital aqueduct stenosis, i.e. branching or forking of the aqueduct between III and IV ventricle, is the commonest cause of congenital hydrocephalus. It is usually caused by intrauterine viral infections (specially mumps), though few cases are inherited (X-recessive) or associated with neural tube defects/neurofibromatosis. Aqueduct stenosis may be rarely acquired following post-meningitic or post-hemorrhagic gliosis.

Dandy-Walker malformation is characterized by *cystic dilation of the IV ventricle* and hydrocephalus *due to atresia of the foramina of Lushka and Magendie*. Agenesis of cerebellar vermis and corpus callosum is frequently associated. Large head with prominent occiput and positive transillumination test on skull are highly suggestive of Dandy-Walker malformation.

Arnold-Chiari malformation, a common cause of congenital hydrocephalus, is of two types:

a. Type II is characterized by—(a) elongation of fourth ventricle, (b) kinking of brainstem, and (c) displacement of inferior vermis, pons and medulla into cervical canal leading to obstruction of subarachnoid pathways and hydrocephalus. Usually associated with myelomeningocele, these cases presents with progressive hydrocephalus in infancy.

b. Type I is less severe, characterized by downward displacement of cerebellar tonsils into cervical canal and usually presents with headache, neck pain, bladder involvement and progressive spastic paraplegia in older children or adults.

TABLE 18.26: Common causes of hydrocephalus

Congenital
- Congenital aqueduct stenosis
- Arnold-Chiari malformations type I and II
- Dandy-Walker malformation
- Vein of Galen malformation

Acquired
- *Post-infectious*—meningitis, intrauterine infections
- *ICSOL*—tumors, tuberculoma, hematoma
- Subarachnoid hemorrhage
- Achondroplasia
- *Pseudotumor cerebri*, e.g. hypervitaminosis A
- ↑*CSF production*, e.g. choroid plexus papilloma

Post-inflammatory exudates *in meningitis are commonest causes of communicating/acquired hydrocephalus.*

Hydrocephalus in Hurler syndrome is due to fibroid tissue proliferation in the subarachnoid spaces, while in achondroplasia, it is due to underdeveloped occipital skull and posterior fossa (platybasia).

Clinical manifestations of hydrocephalus depend on the severity of obstruction and rate of rise in ICP. While few cases are asymptomatic due to slower accumulation of CSF, a typical case presents with:

- ***Progressive enlargement of head*** is the most prominent sign of hydrocephalus in infancy before sutural closure, with bulging anterior fontanel, widening of sutures, dilated veins over scalp, prominent forehead and downward deviation of eyes, i.e. *Sunset sign* **(Fig. 18.8)**. Skull may be translucent in severe hydrocephalus with cortical thinning, e.g. Dandy-Walker malformation. *Macewan sign,* i.e. a cracked-pot sound on percussion of skull, indicates sutural separation in older children, though it is of no diagnostic value in infants with open anterior fontanels. Head size may be normal in mild or early hydrocephalus, developing after the developmental closure of skull sutures.
- ***Raised intracranial pressure (ICP)*** with *headache, irritability, vomiting, papilledema and diplopia*. Papilledema may not be obvious in infancy as raised ICP is released outwards due to open sutures. Optic atrophy due to compression of optic nerve/chiasma may develop in untreated cases. Systemic indicators of raised ICP include *bradycardia, hypertension and irregular respiration,* due to brain-stem compression or autonomic disturbances.
- ***Pyramidal tract involvement***, e.g. spastic paraplegia is common, due to stretching and disruption of the corticospinal fibers, passing in vicinity of dilated lateral ventricles.
- ***Gradual change in personality*** and deterioration in academic achievement might be an early indicator of slowly progressive hydrocephalus with raised ICP.

Fig. 18.8: **Hydrocephalus: Sunset sign.**

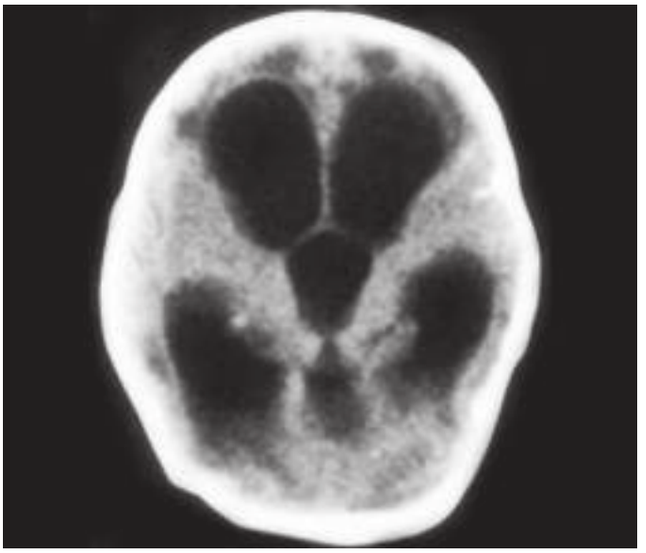

Fig. 18.9: **Hydrocephalus: CT scan showing dilated ventricles with periventricular oozing of CSF.**

- ***Other indicators,*** e.g. disturbances in growth, sexual development and fluid/electrolyte homeostasis may develop in chronic cases due to the pressure of dilated third ventricle on hypothalamus.

Diagnosis is based on clinical findings, supported by following investigations to identify the cause:

- *Neuroimaging* with USG (till AF is open), CT scan or MRI to identify the severity, and specific cause of hydrocephalus, as well as exact location of lesion. In obstructive hydrocephalus, only the ventricular system proximal to the block dilates, whereas in non-obstructive type, entire ventricular system is uniformly dilated **(Fig. 18.9)**. Congenital hydrocephalus can also be detected antenatally on USG.
- *CSF examination* for underlying infection, which should be treated before shunt surgery to avoid complications, e.g. shunt-block or infection.

D/D of hydrocephalus includes other causes of *large head*, e.g. (a) thick cranium, e.g. hemolytic anemia, rickets, etc., (b) subdural hematoma/effusion, (c) hydranencephaly, and (d) megalencephaly.

Megalencephaly, defined as Brain weight:volume ratio >2 SD for age, is usually accompanied by *Macrocephaly*, i.e. head circumference >2 SD for age. Megalencephaly may be primary (benign familial) or secondary, seen in genetic syndromes, e.g. Sotos syndrome, neuronal storage disorders (Ch 18.12), Hurler syndrome and neurofibromatosis.

Management of hydrocephalus aims to control intraventricular pressure by surgical or medical means and treatment of primary cause.

Medical therapy to reduce CSF production with acetazolamide, furosemide and glycerol, is only a temporary measure to arrest further progress of hydrocephalus, indicated in—(a) mild/slowly progressive hydrocephalus, (b) hydrocephalus with CSF infection, till shunt surgery is possible, (c) hydrocephalus due to increased CSF production, e.g. choroid papilloma, and (d) as adjuvant to shunt surgery.

Surgical intervention with creation of a mechanical shunt to facilitate CSF drainage is cornerstone of treatment in moderate to severe hydrocephalus. Although various shunt procedures draining ventricular system extracranially (into peritoneum, atrium, jugular veins) or intracranially (to the ventricle distal to block site) have been used, *ventriculoperitoneal shunt (VP)* continues to be the procedure of choice in most cases. Commonly used VP shunts have non-return, pressure-limited valves, which drain excess CSF into peritoneal cavity whenever intraventricular pressure rises above a critical level.

Shunt surgery should be deferred till normalization of CSF in subarachnoid hemorrhage or meningitis, as high protein content of CSF may block the shunt. These cases may be temporarily treated by placing a temporary reservoir in the ventricle through which repeated CSF tapping can be done.

Complications of shunt surgery include—(a) shunt block, (b) shunt infection, usually caused by *Staph. epidermidis*, (c) shunt displacement/extrusion, (d) shunt fracture, (e) peritonitis and (f) skin/subcutaneous infection or abrasion over the shunt track.

To avoid the complications of shunt, ***endoscopic third ventriculostomy*** is being done increasingly in which an endoscope is passed through laternal ventricle and a perforation is made in the floor of third ventricule to allow drainage of CSF directly from ventricles to the subarachnoid space.

Prognosis depends on the cause and size of ventricles, along with thickness of cortical mantle at the time of operative intervention. Hydrocephalic children are at risk for developmental disabilities, visual field defects, optic atrophy and intellectual and motor handicaps.

18.11 CEREBRAL PALSY

Cerebral palsy (CP) is non-progressive neuromotor deficit of cerebral origin due to antenatal, perinatal or early postnatal insult of the developing brain, more precisely defined as *"a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain"*.

Mental retardation, although present in >50–75% cases, is not an essential feature of CP.

Incidence: CP is the commonest cause of motor handicap in Indian children after control of poliomyelitis, with estimated prevalence of ~ 2/1000 live births.

Despite major improvements in perinatal care during recent years, incidence of CP has not declined due to increasing survival of high-risk neonates, e.g. preterm and low birth weight.

Etiology: Brain growth is nearly complete by 2 years of age. CP is a clinical manifestation of developing brain injury during this period, irrespective of the cause, commonest being the adverse perinatal event, e.g. *prematurity and birth asphyxia*. Important etiological factors for CP include:

- *Prenatal causes* (20%)
  - Congenital brain malformations
  - Intrauterine infections
  - Intrauterine hypoxia
  - Maternal exposure to toxins
- *Perinatal causes* (70%)
  - Prematurity
  - Birth asphyxia
  - Birth trauma/injury
- *Postnatal causes* (<10%)
  - Kernicterus
  - Neonatal meningitis, septicaemia or stroke
  - Prolonged hypoglycemia

Clinical manifestations of CP range from minor motor incapacitation to crippling handicaps, depending on the extent, site and timing of neurological injury. While it is a static neurological defect, signs may evolve over a period of time with maturity of brain and full clinical picture of handicap may not be obvious till late infancy. According to the clinical neurodeficit, CP is classified into five main categories:

a. Spastic (60–70%)
b. Extrapyramidal (~20%)

Fig. 18.10: Scissoring in spastic cerebral palsy.

c. Ataxic/cerebellar (<5%)
d. Atonic (rare)
e. Mixed (10–15%)

a. Spastic CP is the commonest type, representing cortical or pyramidal tract injury and mostly seen in preterms or following birth asphyxia. Depending on the topographic distribution, spastic CP is further classified as *quadriplegia, diplegia, hemiplegia or monoplegia*.

Spastic diaplegia, i.e. quadriparesis with more prominent involvement of lower limbs than upper limbs, is more common in preterms due to higher incidence of periventricular leukomalacia. Periventricular lesions mainly affects medially located nerve fibers in pyramidal tracts, which supply lower limbs. Important signs of spastic CP include:

- ***Abnormal tone:*** Hypotonia is common in neonatal period, which gradually evolves into intermittent dystonia and then the spasticity, presenting with:
  - *Clasp-knife spasticity* in involved limbs,
  - *Scissoring* of legs due to persistent spasm of adductor muscles **(Fig. 18.10)**,
  - *Commando-crawl* due to spastic, extended lower limbs,
  - Restricted joint mobility, e.g. reduced popliteal angle and ankle dorsiflexion,
  - Intermittent dystonia with arching of back/neck and stiffening of limbs, and
  - Decreased spontaneous movements of body, e.g. hand-swing during walking. Difficulty in changing the diaper may be an early indicator of hypertonia in spastic CP.
- ***Abnormal gait and posture*** due to abnormal tone or contractures, which may also cause shortening of limbs and present with:

  - Postural distortions, which tends to worsen during activity or excitement,
  - Hemiplegic gait or *Commando-crawl* (dragging of feet while crawling), and
  - *Cortical thumb* with hyperextension at metacarpophalangeal joint and flexion at interdigital joint
- ***Abnormal reflexes*** **including:**
  - Persistence of neonatal reflexes, and
  - Hyerreflexia, clonus and positive Babinski sign.
- ***Abnormal function*****, e.g.**
  - Feeding difficulties with *sialorrhea* and recurrent aspiration due to pseudobulbar palsy and gastroesophageal reflux,
  - Dysarthria due to palatopharyngeal incoordination,
  - Delayed motor development due to tone and posture abnormalities.
- ***Associated abnormalities*** include mental retardation (~50%), seizures (~33%), visual/hearing impairment and subtle sensory defects, e.g. stereognosis.

b. Extrapyramidal CP, also termed as Athetoid or Dyskinetic CP, represents basal ganglia injury, usually following kernicterus. These cases presents with: *(a) lead-pipe rigidity, (b) dystonia, (c) choreo-athetoid movements,* and *(d) dysarthria*. Unlike spastic diplegia, upper extremities are generally more affected than lower extremities in extrapyramidal CP.

Hearing impairment is very common but intellect is relatively preserved. Incidence of extrapyramidal CP has declined in recent years due to aggressive management of neonatal hyperbilirubinemia.

c. Ataxic CP denotes cerebellar malformations or involvement, presenting with—(a) *hypotonia*, (b) *hyporeflexia* (Note: only CP with hyporeflexia), and (c) *ataxia with intention tremors*, by 2–3 years of age. Mental retardation is uncommon.

d. Atonic CP is extremely rare, presenting with *unusual combination of hypotonia with brisk reflexes*. Severe mental retardation is common.

Diagnosis: Early diagnosis of CP is essential to achieve maximum functional potential and it is usually possible to suspect it by 3 months of age. Early indicators of CP **(Table 18.27)** should be specially looked for during follow-up of high-risk newborns at 6 weeks, 3 months, 6 months and 1 year. Investigations primarily aim to detect comorbidities, which may further contribute to child's handicaps.

All cases need—(a) EEG to detect underlying seizure disorders, (b) hearing assessment by BERA test, and (c) assessment of vision.

Neuroimaging (CT/MRI), though not essential for diagnosis, may reveal cerebral atrophy, infarcts, leukomalacia and dilated ventricles, etc. Select cases with family history also require chromosomal studies or plasma/urine chromatography for inborn errors of metabolism.

TABLE 18.27: Early indicators of cerebral palsy

Newborns
- High-risk perinatal history
- Unexplained feeding difficulties
- Asymmetric limb movements or Moro's response
- Spontaneous startle response
- Episodes of inconsolable cry
- Difficulty in changing diapers (hypertonia)

Early infancy
- Delayed early milestones, e.g. neck holding
- Abnormal persistence of neonatal reflexes
- Stereotype movements, e.g. chewing, lip smacking
- Paucity of fidgety limb movements >6–12 weeks
- Abnormal posture, tone, reflexes (see text)
- Persistence of cortical thumb >8 weeks
- Slower growth in head size

Management of CP needs a holistic team-approach, with an ***aim*** to achieve the maximum functional status and independent life despite physical handicaps. Important components of care include:

a. Physiotherapy is the cornerstone of therapy in CP, which should be started as early as possible to prevent contractures and maximize functional achievement. Various specialized techniques, e.g. *Vojta's method* are commonly used to relax contralateral group of muscles in these cases.

CIMT (*Constraint induced movement therapy*) is commonly used to improve functions of the affected hand based on the principle that restricting the use of good hand forces use of affected hand and improves its function by neuroplasticity of the brain.

b. Orthotic support with splints and braces are usually necessary for mobility, though splinting should not prevent physiotherapy. Orthopedic correction of postural deformities/contractures may be necessary before orthotic support in some cases.

c. Muscle relaxants, e.g. PO Clonazepam (0.01–0.1 mg/kg/day), *Baclofen* (0.2–2.0 mg/kg/d q12hr) or *Dantrolene* (0.5–2 mg/kg/d q12hr) can be used to treat spasticity in selected cases. Intrathecal baclofen via an implanted pump has been used successfully in cases with severe spasticity. Use of local *botox* (botulinum toxin) infiltration to relieve spasticity, is specially useful in spastic diplegia and hemiplegic cerebral palsy, to be used only after 2 years of age.

Selective dorsal rhizotomy, i.e. cutting of 25–60% of dorsal roots at L_2-S_1 level to decrease muscle tone in corresponding extremity at 2–7 years has been reported as beneficial in diplegia, though risk of complete paralysis precludes it routine use.

d. Treatment of co-existing defects in hearing, speech and vision is the priority in CP to maximize functional potential. Anticonvulsant therapy may be required but prophylactic anticonvulsants are not indicated.

Choreo-athetoid movements may be controlled with PO Tetrabenazine (6.25 mg BD, maximum 50 mg/day) and/or Clonazepam (0.01–0.1 mg/kg/day). Severe dystonia may be treated with PO Trihexyphenidyl (0.25 mg/day q12h) and/or Levodopa (1–5 mg/kg/day).

e. Occupational therapy in early life aims to maximize independence in day-to-day activities, e.g. feeding, dressing, etc., while suitable vocational skills, e.g. typing, may be offered to older children for financial independence.

f. Psychological support and motivation to the patient, parents and family is vital for successful adaptation of these children within their functional limits. Community awareness is equally important to accept and support these cases.

g. Institutional care is the last resort, reserved for seriously handicapped children.

18.12 INTRACRANIAL INFECTIONS

Intracranial infections may be generalized or localized. Generalized CNS infections may be further classified depending upon the predominant involvement of meninges (meningitis), brain parenchyma (encephalitis) or both (meningoencephalitis).

Common localized infections include brain abscess, tuberculoma or neurocysticercosis. CNS may also be involved in other systemic infective illnesses, e.g. cerebral malaria and enteric fever.

18.12.1 BACTERIAL MENINGITIS

Bacterial meningitis (BM) is a potentially life-threatening CNS infection, characterized *by primary inflammation of leptomeninges* due to non-tubercular bacterial infections.

Epidemiology: BM is more common in children <5 years. Important ***risk factors*** include—(a) ENT infections, e.g. otitis media, mastoiditis or sinusitis, (b) neural tube defects, (c) head injury, (d) foreign body, e.g. CSF shunts, (e) splenic dysfunction, e.g. asplenia or splenectomy, (f) immunodeficiency disorders.

Recurrent meningitis may be seen in cases with—(a) CSF rhinorrhea following skull fractures involving cribriform plate or ethmoidal sinus, (b) lumbosacral dermal sinus, and (c) immunodeficiency disorders.

Etiology: Microbiology of BM depends on the age, source of infection and host-defence, as follows:

- *In newborns and first 3 months* of life, BM is usually caused by organisms from maternal flora, commonest being *E. coli, Staph. aureus* and enterococci (*S. fecalis*). *Listeria monocytogenes* is emerging as common pathogen in this age group. Group B streptococci, a common cause of neonatal meningitis in western countries, is uncommon in India.
- *From 3 months to 3 years; H. influenzae B* (HiB) is the commonest cause (~50%), followed by *S. pneumoniae, Staph. aureus* and *N. Meningitides* (usually in outbreaks). Incidence of Hib meningitis has declined due to widespread immunization.
- *In older children >3 years; S. pneumoniae* is the predominant pathogen, write *N. meningitides* is common during outbreaks.
- *Nosocomial or opportunistic meningitis* may be caused by any prevalent hospital flora, e.g. *Staph. aureus*, coagulase-negative staphylococci, Pseudomonas, Klebsiella, Candida, etc.

Certain pathogens are more common in high-risk children, e.g. pneumococci in cases with ENT infections and CSF leak; capsular organisms like pneumococci, Hib and meningococci in splenectomized children; *Staph. epidermidis* in ventriculoperitoneal shunts; and Cryptococcal or Listeria meningitis in immunodeficiency disorders.

Pathogenesis: Causative organisms reach the meninges via—(a) hematogenous spread from a distant septic focus, or (b) direct spread from colonized nasopharynx or neighboring infection, e.g. otitis media, cranial trauma or menigomyelocele. Inflammation of meninges initiates multiple pathological reactions, as follows:

- *Extensive meningeal exudates*, which tend to collect at the base of brain and block subarachnoid space, leading to hydrocephalus.
- *Vasculitis and thrombosis* of cerebral vessels, leading to parenchymal infarcts with localizing signs and residual sequelae.
- *Cerebral edema*, which may be *vasogenic* due to direct endothelial injury and increased vascular permeability or *cytotoxic* due to release of various chemical mediators, e.g. cytokines.
- *Raised ICP* due to-i) cerebral edema, (ii) CSF flow block, and (iii) water retention due to inappropriate ADH secretion (SIADH).
- *Ventriculitis*, leading to persistence of infection is more common in newborns and infants.

Clinical presentation depends on the age and causative organism, being more severe and acute in young and immunocompromised children. A typical case of BM presents with *acute onset* (usually < 72 hours) of:

- *High fever* with constitutional signs, e.g. irritability/lethargy and anorexia.
- *Signs of meningeal irritation*, e.g. nuchal rigidity, Kernig's sign and Brudzinski's sign, though these signs are uncommon in infants.
- *Signs of raised ICP*, e.g. headache, vomiting, bulging anterior fontanel, widening of cranial sutures and

papilledema. irregular breathing, hypertension and bradycardia.
- *Altered sensorium* and coma due to cerebritis and cerebral edema, along with decerebrate or decorticate posture.
- *Focal neurological signs*, e.g. cranial nerve palsies and motor deficits, are less common in BM (15–30%) than in tubercular meningitis.
- *Seizures or status epilepticus* due to cerebritis, infarcts and electrolyte disturbances (SIADH).

Unique features of BM due to specific organisms are as follows:

Hib meningitis is most common in 6 months – 2 years age group *or* in older children with splenic dysfunction. Subdural effusion is common, leading to persistent fever and neurological signs despite CSF clearance.

Meningococcal meningitis is usually seen in epidemics due to group A and C infections, while group B infections cause sporadic disease. Presence of petechial rash over skin/mucus membranes or circulatory shock (due to adrenal hemorrhage; *Waterhouse-Friderichsen syndrome*) is a strong indicator of meningococcal disease.

Pneumococcal meningitis is more common beyond infancy, frequently associated with ENT infections, head injury or splenic dysfunction, e.g. sickle cell disease. Subdural effusions are common.

Staphylococcal meningitis is common in newborns and young children with obvious septic focus, e.g. pneumonia or osteomyelitis. Toxic look, fulminant course and focal neurological signs due to sinus thrombosis are common.

Diagnosis of BM depends on:
- ***Clinical suspicion*** in a case with fever and neurological signs. Diagnosis is difficult in young infants due to absence of high fever and signs of meningeal irritation due to limited inflammatory response. Presence of neonatal sepsis (Ch 12.15.2) with—(i) vacant stare, (ii) seizures, (iii) irritability or drowsiness, and (iv) altered tone, should arouse suspicion of BM in this age group.
- ***CSF examination*** is baseline investigation in BM after excluding contraindications (Ch 18.2), revealing—(a) increased pressure (b) turbid appearance, (c) markedly high proteins (>200 mg/dl), (d) severe hypoglycorrhoea, (CSF glucose <50% of blood glucose), and (e) marked polymorphonuclear pleocytosis (>200 cell/mm^3). However, CSF findings in partially-treated cases or traumatic LP may be misleading due to altered biochemical/cellular values.
- ***CSF microbiology:*** Identification of causative pathogen in CSF by gram-staining and culture is essential for rational antimicrobial therapy, though it may be sterile after prior antibiotic therapy. *Blood culture* may help to identify causative pathogen in such cases.
- ***Rapid diagnostic tests*** for causative pathogens in CSF are available, to detect presence of specific *antigens* (latex-agglutination test) or microbial *DNA (PCR)*. These tests are specially useful to diagnose BM in partially treated cases.
- ***Neuroimaging*** with CT/MRI is necessary in non-responders or those with low GCS (<12), status epilepticus, and/or focal signs to exclude complications, e.g. hydrocephalus, subdural effusions/empyema, cerebral infarcts, etc.
- ***Ancillary investigations,*** e.g. S. electrolytes (for SIADH) may be needed in some cases.

D/D of BM mainly includes:
- *Meningism* in apical pneumonia or inflammatory lesions of neck (normal CSF with no neurological findings except neck rigidity),
- *Tubercular meningitis* (see **Table 18.30)**
- *Viral encephalitis* (very acute onset, no signs of meningeal irritation, sterile CSF).
- *Aseptic meningitis* (clinical picture and CSF findings suggestive of BM, with sterile CSF).
- *Cerebral malaria* (normal CSF and positive peripheral smear for parasites).

In addition, BM may also be confused with other causes of coma and seizures, including subarachnoid hemorrhage (no fever, hemorrhagic CSF) and focal CNS infections, e.g. brain abscess (localizing signs).

Management of BM includes—(a) specific antimicrobial therapy, and (b) supportive therapy.

I. Antimicrobial therapy: Empirical therapy with broad-spectrum IV antibiotics should be started immediately in all cases, which must be modified after culture and sensitivity reports are available. Choice of the antibiotics depends on probable cause and local microbial profile, modified after culture/sensitivity reports **(Table 18.28)**.

After initiation of effective antibiotic therapy, CSF turns sterile within 24 hours and clinical response is obvious within 48–72 hours. Repeat CSF analysis is not necessary, indicated only in non-responsive cases after 48 hours.

Antibiotics should be continued IV for minimum 10–14 days (except in meningococci for 7 days and gram-negative meningitis for 21 days) *or* till the patient is afebrile for minimum 3–5 days.

II. Supportive therapy in BM includes:
- *Continuous monitoring* and management of hypotension, shock and respiratory problems.
- *Parenteral fluid therapy* to correct fluid/electrolyte imbalance and provide nutrition. Only 2/3rd of calculated fluid requirement should be given, as SIADH is present in 60–70% cases.

TABLE 18.28: Antimicrobial therapy in bacterial meningitis

Age/organism	*Drugs of choice*
A. Empirical therapy	
Neonates	Ampicillin + Cefotaxime or Aminoglycoside
Older children	TGC + Vancomycin
High-risk cases	Vancomycin + Cefepime/ Ceftazidime
Head injury/Neurosurgery	
B. Specific therapy	
H. Influenzae	Ceftriaxone
S. pneumoniae	Penicillin or TGC+Vancomycin
N. meningitides	Penicillin or TGC
Gram –ve pathogens	TGC + Aminoglycoside
Pseudomonas	TGC + Aminoglycoside
Staph. aureus	Cloxacillin or Vancomycin
Listeria monocytogenes	Ampicillin

High-risk cases: Head injury, neurosurgery, CSF-Shunt
TGC: 3rd generation cephalosporins, e.g. ceftriaxone, cefotaxime or ceftazidime
Antibiotic doses in meningitis are usually higher than those for other indications, as follows:
Ampicillin (200–400 mg/kg/d), Amikacin (15 mg/kg/d), Gentamycin (6–8 mg/kg/d), Penicillin (3,00,000 IU/kg/d), Vancomycin (60 mg/kg/d), Ceftriaxone (100 mg/kg/d), Cefotaxime (200 mg/kg/d), Ceftazidime (150–200 mg/kg/d), Cefepime (50 mg/kg/d)
All drugs are given IV; and in 3 divided doses, except penicillin (in 4–6 divided doses)

- *Treatment of raised ICP* with IV 3% hypertonic saline or mannitol (Ch 18.4). Mannitol infusion may be necessary even before lumbar puncture in suspected case of raised ICP.
- *Treatment of seizures* with IV Midazolam (0.2 mg/kg), followed by long-term anticonvulsants, e.g. phenytoin or phenobarbitone. Prophylactic anticonvulsants, even in absence of seizures, are indicated during acute phase of BM.
- *Steroids*, e.g. Dexamethasone (0.15 mg/kg/dose 6-hourly 2–3 days) may be useful to reduce cerebral edema and inflammation as well as to improve antibiotic penetration. While exact role of steroids in BM is controversial, available evidence support their value in cases with focal signs to reduce the risk of complications, e.g. hearing loss or hydrocephalus. However, steroids may be useful only if given within first 4 hours of antibiotic therapy.
- *General nursing care* to prevent aspiration, bed sores and bladder/bowel retention along with symptomatic treatment for fever, etc.
- *Treatment of complications*, e.g. hydrocephalus, subdural effusion or ventriculitis, which are likely in non-responding cases and needs to be excluded by neuroimaging.

  Subdural empyema is common in *H. influenzae* meningitis and may need neurosurgical intervention with repeated tapping or burr-hole drainage, with longer course of antibiotics for 4–6 weeks.

  Ventriculitis may need repeated ventricular tapping, preferably after placement of *Ommaya reservoir*, with or without intraventricular instillation of antibiotics. *Shunt placement is rarely required. If necessary, shunt surgery in BM should be deferred till CSF is abnormal, due to risk of shunt block and infection*.

Outcome: With early and appropriate antimicrobial therapy, mortality in BM is <10%, though 10–20% of recovered cases may develop neurodevelopmental *sequelae*, e.g. (i) intellectual disability or learning disabilities, (ii) secondary epilepsy, (iii) focal motor deficits, and (iv) hearing, visual or speech impairment. Hydrocephalus is uncommon in BM.

Sensorineural hearing loss is the commonest sequelae of BM, specially in cases with—(a) age <6 months, (b) peumococcal meningitis, (c) high CSF bacterial count, (d) persistent seizures/coma despite 72–96 hours of antibiotics.

Repeated episodes of BM may be due to—(a) *recrudescence*, i.e. resurgence of infection during therapy due to secondary drug resistance, (b) *relapse* after 3–21 days of completed therapy due to persistent focus, e.g. ventriculitis, subdural empyema or cerebral abscess and (c) *recurrence* due to anatomical/immunological defects.

Prevention of BM involves—(a) routine vaccination against Hib and PCV, (b) vaccination for meningococci in high-risk children, and (c) rifampicin prophylaxis in contact of meningococcal carriers/contacts (Ch 10.10).

18.12.2 TUBERCULAR MENINGITIS

CNS involvement is the second most severe complication of tuberculosis after miliary tuberculosis, responsible for 60–70% of all TB-related deaths in children. Tuberculosis may involve any part of CNS, with wide spectrum of presentations **(Table 18.29)**.

Tubercular meningitis (TBM) is the commonest manifestation of neurotuberculosis with high mortality and residual morbidity in survivors, discussed here.

Epidemiology: TBM is most common between 6 months – 3 years of age, with following ***risk factors***—(i) BCG unimmunized child, (ii) low socioeconomic status, (iii) severe malnutrition, (iv) history of contact, (v) recent immunosuppressive illnesses, e.g. measles, pertussis, etc., and (vi) immunodeficiency states, e.g. HIV.

Pathogenesis: Tubercular infection of brain is usually caused by hematogenous spread from primary focus. Rarely, it may also reach from cervical lymph nodes via transcranial connecting lymphatics.

Hematogenous infection tends to be typically trapped in end-arteries to form a sub-meningeal cortical focus (*Rich's focus*), which may remain—(a) silent, (b) progress locally to form tuberculoma and present as a space occupying lesion, or (c) rupture over meninges to cause TBM.

TABLE 18.29: Types of neurotuberculosis

- **Intracranial**
  - Tubercular meningitis
  - Tubercular encephalopathy
  - Tuberculoma
  - Aseptic (Lincoln's) meningitis
- **Spinal**
  - Arachnoiditis
  - Tuberculoma
  - Compressive myelopathy
  - Polyneuropathy

Pathological characteristics in TBM include:

- *Meningeal exudation* due to intense inflammatory reaction, which is most prominent on base of the brain (*basal exudates*) and may lead to—(i) infranuclear cranial nerve palsies by entrapment of nerves, and/or (ii) communicating hydrocephalus due to impairment of CSF absorption in arachnoid villi.
- Parenchymal *Endarteritis obliterans*, due to perivascular inflammation, leading to infarcts and focal signs.
- *Choroidal tuberculoma and exudates*, blocking CSF flow to cause obstructive hydrocephalus.
- *Cerebral edema* and impairment of blood-brain barrier, leading to altered sensorium, raised ICP and CSF abnormalities.

Clinical presentations are extremely variable, though a typical case presents with three stages:

1. ***Prodromal stage*** *(stage of invasion)* with insidious onset of fever, constitutional symptoms and signs of raised ICP, e.g. headache, vomiting, irritability and papilledema.
2. ***Stage of meningitis*** with—(a) signs of meningeal irritation, e.g. neck rigidity, Kernig's sign, etc., (b) seizures (c) focal neurodeficits, e.g. hemiplegia.
3. ***Stage of coma*** with—(a) loss of consciousness, (b) decerebrate/decorticate posture **(Fig. 18.11A)** and (c) altered vital functions, e.g. irregular respiration, hypo/hypertension, etc.

While each stage lasts for ~1–2 weeks, illness may progress rapidly without clear distinction of stages.

Atypical TBM may also present as: (a) pyrexia of unknown origin, (b) acute stroke, e.g. hemiplegia, (c) slowly progressive encephalopathy, (d) intracranial space occupying lesion, (e) recurrent seizures, (f) hysteria, (g) hydrocephalus, or (h) isolated cranial nerve palsies.

Diagnosis of TBM is based on:

- *Clinical indicators*, e.g. (i) risk factors, (ii) history of contact, (iii) insidious clinical course;
- *Supportive evidences*, e.g. positive tuberculin test and/or X-ray chest.
- *CSF examination* reveals straw-color CSF **(Fig. 18.11B)**, cobweb formation, moderately raised proteins and cells (mainly lymphocytes) and mild *hypoglycorrhachia* **(Table 18.6)**.
- *Microbial confirmation from CSF with positive* (i) AFB staining, (ii) microbial culture, (iii) molecular diagnosis, as discussed in Ch 10.13. X-pert MTB-RMP (GeneXpert) not only to detect the organism but also the rifampicin sensitivity and results are available in 2 hours.
- *Neuroimaging with CT/MRI* is highly informative, showing basal exudates, infarcts and hydrocephalus **(Fig. 18.12)**.

Serological tests for TB antigen or antibodies or interferon assays have no place in diagnosis. However, elevated levels of *adenosine deaminase* and *tuberculostearic acid* in CSF-metabolites produced by degradation of lymphocytes and TB bacilli respectively, support the diagnosis of TBM.

Fig. 18.11A: Tubercular meningitis: (A) Decerebrate posture.

Fig. 18.11B: Tubercular meningitis: (B) Straw-color CSF with Cobweb information.

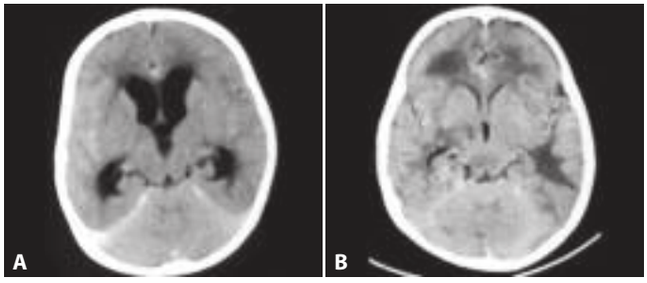

Fig. 18.12A and B: Tubercular meningitis–CT scan showing: (A) Basal exudates with hydrocephalus; (B) Infarct.

D/D: TBM should be considered in d/d of any acquired CNS disease in endemic region. Common illnesses mimicking TBM include—(a) bacterial meningitis **(Table 18.30)**, (b) encephalitis, (c) cerebral malaria, (d) enteric encephalopathy, and (e) intracranial space occupying lesions.

Management of TBM includes:

- ***Specific anti-tubercular therapy:*** As per NTEP recommendation for drug-sensitive neurotuberculosis, four drugs are used in intensive phase for 2 months followed by a continuation phase of 10 months with three drugs (2HRZE+10 HRE). While treatment of TBM should not be delayed for want to sensitivity results, it must be modified accordingly once the reports are available (Ch 10.13).
- ***Steroids,*** i.e. PO Prednisolone (1–2 mg/kg/d q6–8hr) for 6 weeks before gradual tapering are indicated in all cases to reduce inflammation and cerebral edema as well as to improve CSF penetration of drugs. Initially, IV steroids, e.g. hydrocortisone or dexamethasone may be used in acutely sick cases.
- ***Supportive therapy*** with:
  - Nutrition and fluid/electrolyte maintenance.
  - Constant monitoring and cardiorespiratory support
  - Anti-edema measures, e.g. mannitol, hypertonic saline, acetazolamide, glycerol, etc. Steroids also act as anti-edema agents.
  - Anticonvulsants, even in absence of seizures.
  - Prophylactic antibiotics for initial 1–2 weeks, as it is often difficult to exclude pyogenic etiology.
  - Physiotherapy, as soon as possible.
  - Shunt surgery for hydrocephalus is commonly required in most cases of TBM.

Outcome of TBM depends on the clinical severity of disease on admission and appropriateness of treatment. Early diagnosed cases (stage I) have best prognosis with rare deaths and residual sequelae (<10%). Risk of mortality and residual lesions is high, i.e. 20–50% and 50–80% in stage II and III disease respectively.

Outcome is poor in cases with—(a) age <2 years, (b) severe malnutrition, (c) coma, seizures or focal signs on admission (d) severe hydrocephalus and (e) poor therapeutic response in initial weeks.

Common *sequelae* of TBM are: (a) hydrocephalus, (b) secondary epilepsy, (c) focal motor deficits, e.g. hemiplegia, (d) mental retardation, (e) vision or hearing loss, (f) speech defects, and (g) endocrinal problems, e.g. obesity, diabetes insipidus, etc.

TABLE 18.30: D/D between BM and TBM

Features	*BM*	TBM
Clinical:		
Common age	Infancy	>6 months
History of contact	–	Common
BCG vaccination	Yes	Often absent
Nutritional status	Good	Poor
Septic focus	Present	Absent
Onset/Progression	Rapid	Gradual
Focal signs	Uncommon	Common
Toxemia	Present	Absent
CSF Exam:		
Appearance	Turbid	Straw-color
Cobweb formation	–	+
Proteins	↑↑	–
Sugar	↓↓	↓
Cells	↑↑(Poly)	↑↑(Lympho)
Microbiology	Gm staining	AFB staining

18.12.3 VIRAL ENCEPHALITIS

Encephalitis *refers to acute inflammatory injury of the brain parenchyma,* while the term ***Encephalopathy*** *denotes generalized cerebral dysfunction due to non-inflammatory causes*, e.g. metabolic, hypoxic, ischemic or toxic states.

Acute encephalitis syndrome **(AES)** is a term coined by WHO for surveillance purpose, specially in context of Japanese encephalitis, to include *any case irrespective of the age or season with acute onset of fever with change in mental status and/or new onset of seizures* **(Table 18.31)**.

Etiology: Encephalitis may be infective or non-infective in origin. While non-infectious encephalitis is usually of autoimmune eiology (Ch 18.12.4), infective encephalitis is mostly viral in origin, caused in India by:

- *Enteroviruses* in >80% cases, during epidemics.
- *Herpes simplex* (HSV_1) – commonest cause of sporadic encephalitis.
- *Arboviruses*-Japanese B encephalitis, as small outbreaks.

Other viral illnesses, e.g., mumps, measles, varicella, dengue, rubella, EBV, influenza viruses and rabies are responsible for sporadic cases. CMV infections cause encephalitis in neonates or immunocompromised hosts.

TABLE 18.31: Causes of acute encephalitis syndrome

Infective
- *Viral:* HSV, JE, enteroviruses, measles, ARBO viruses
- *Bacterial:* BM, TBM, enteric fever
- *Spirochetal:* Leptospirosis
- *Others:* Rickettsial fevers, toxoplasmosis

Autoimmune encephalitis
- Acute disseminated encephalopathy (ADEM)
- ANMDAR encephalitis

Metabolic
- Reye syndrome
- Hepatic/renal failure
- Diabetic ketoacidosis
- Dyselectrolytemia, lactic acidosis, IEM

Toxic: Poisonings, e.g. lead, carbon monoxide
Hypoxic-ischemic encephalopathy
Vascular: Hypertension, strokes
Traumatic: Head injury
Hereditary: Mitochondrial encephalopathies

HSV: Herpes simplex; **JE**: Japanese encephalitis; **ARBO**: Arthropod-borne; **ANMDAR:** Anti-n-methyl-d-aspartate receptor encephalitis; **IEM:** Inborn errors of metabolism

Epidemiology of viral encephalitis is essentially the epidemiology of causative viral disease, which may be sporadic or epidemic. Epidemics are common during or immediately after rainy season.

Pathogenesis: Neurological damage in encephalitis may be due to—(a) *direct* invasion and destruction of neural tissues by actively multiplying viruses, or (b) *hypersensitivity reaction* to viral antigens, leading to demyelination and perivascular destruction.

Clinical features: Despite the variable etiology, viral encephalitis usually presents after a short non-specific prodromal viral illness with *acute* onset of: (a) high fever, (b) altered sensorium with progressive coma, (c) recurrent seizures or status epilepticus, and (d) signs of raised ICP, e.g. vomiting, headache, papilledema. *Focal neurological signs are uncommon, except in HSV encephalitis*.

Milder cases may have a more gradual onset with altered behavior and speech, ataxia and abnormal movements, e.g. tremors or choreo-athetoid movements. Exanthems often precede or accompany the CNS signs in viral encephalitis.

Diagnosis is essentially clinical, after exclusion of other CNS infections, e.g. meningitis, cerebral malaria, etc. and non-viral encephalopathies **(Table 18.31)**. Supportive investigations include:
- *Normal CSF examination* except elevated pressure and mild pleocytosis,
- Gross cerebral edema on CT/MRI and,
- Abnormal EEG with diffuse slowing (focal in HSV encephalitis).

Etiological diagnosis is difficult in resource-poor settings, requiring detection of causative virus on CSF culture or PCR. Viral antibody titers turn positive after many weeks with little use in clinical practice, except for epidemiological purpose.

Some useful diagnostic clues include presence of focal signs (HSV), ataxia (VZV), rash (Measles or VZV), diarrrhea (Enteroviruses), respiratory illness (Influenza, adenovirus), parotitis (Mumps) and retinitis (CMV).

Treatment is largely supportive and includes:
- Hospitalization with constant monitoring.
- Resuscitation and life-support measures.
- Correction of fluid and electrolyte disturbances.
- Management of cerebral edema.
- Anticonvulsant therapy.
- Prophylactic antibiotic therapy for suspected bacterial etiology.

Role of *Specific antiviral therapy* is limited, except acyclovir therapy in HSV encephalitis. Immunotherapy with steroids or IVIG must be considered only in cases with suspected autoimmune etiology.

Outcome depends on clinical severity of the disease, age of the patient and efficacy of supportive therapy. Mortality in severe cases may be as high as >50%, while survivors may be left with *residue* like-(a) seizure disorder, (b) deafness/blindness, (c) mental retardation, (d) motor deficits, and (e) behavior disorders.

Some important causes of viral encephalitis in childhood are as follows:

Japanese encephalitis (JE) has emerged as a major public health problem in India during last two decades, with many seasonal outbreaks in different parts of country, specially in Northern India.

Epidemiology: JE virus is a RNA virus, transmitted by *Culex* – a night-biting mosquito. Children are more affected than adults.

Clinically, apart from other signs of acute encephalitis, two important characteristics of JE are: (a) rapidly changing CNS signs, i.e. alternating hyper/hyporeflexia or extensor/flexor planters, and (b) frequent presence of concomitant proteinuria.

Diagnosis depends on epidemiological risk and serology with elevated specific IgM titers in CSF or serum. Viral isolation or detection by PCR from CSF is possible but with very low sensitivity.

Treatment is supportive and non-specific. Prognosis is poorer in children than in adults, with 30–40% mortality and ~40% late neurological sequelae.

Prevention is possible with JE vaccine with two doses at least one-month apart, provided under NIS to all children residing in endemic districts at the age of 9–12 months and 16–24 months, with catch-up immunization (two doses at one month interval) till 15 years of age or even more in some states (Ch 9.2.2).

Herpes encephalitis (HSV1) is the commonest cause of sporadic encephalitis in Indian children, frequently but not essentially, characterized by—(a) localizing signs including focal seizures, (b) focal slowing with periodic lateralized discharges on EEG, (c) focal temporal lobe involvement of CT/MRI and (d) presence of RBCs in CSF.

Specific antiviral therapy with acyclovir (IV 20 mg/kg/dose TDS for 21 days) is highly effective in reducing the mortality and morbidity of these cases.

18.12.4 AUTOIMMUNE ENCEPHALITIS

Autoimmune encephalitis (AIE) includes many clinical syndromes associated with antibodies against neuronal cell surface proteins and intracellular antigens. In ~50% cases, exact antigen and specific antibodies are not yet identified (seronegative AIE).

While exact trigger for development of these antibodies is unknown, many cases are associated with tumors (paraneoplastic) or preceding viral-like illness (parainfectious). AIE of paraneoplastic origin is uncommon in children.

Some important autoimmune encephalitis are as follows:

Acute disseminated encephalomyelitis (ADEM) is the commonest non-infective encephalopathy in children, presenting with acute onset multifocal neurological deficits, due to diffuse and extensive demyelination of brain and spinal cord.

Etiologically, ADEM is considered as an autoimmune response to preceding viral infections or vaccines. Most cases present after 1–2 weeks of non-specific infections, e.g. influenza, varicella, enteroviruses, measles, mumps, rubella, etc. or some vaccinations, e.g. rabies, MMR, DPT, influenza, etc.

Clinically more common 5–8 years age-group, ADEM generally presents with low-grade fever, headache and vomiting, followed by gradual onset of altered sensorium and focal neurological deficits. Seizures, visual loss, cranial neuropathies and bladder/bowel dysfunction may be present.

Diagnosis rests on MRI *showing large, multifocal edematous mass-like tumefactive lesions in white matter* though gray matter and spinal cord may also be involved **(Fig. 18.13)**. Lesions typically appear to be of same age but their evolution may lag behind the clinical presentation.

CSF is normal or may reveal mild lymphocytic pleocytosis. About 10–20% cases have other CSF abnormalities, e.g. oligoclonal bands, raised immune globulin levels or antibodies against myelin oligodendrocyte glycoprotein or aquaporin-4 antigen.

EEG often shows generalized slowing with/without focal epileptiform discharges.

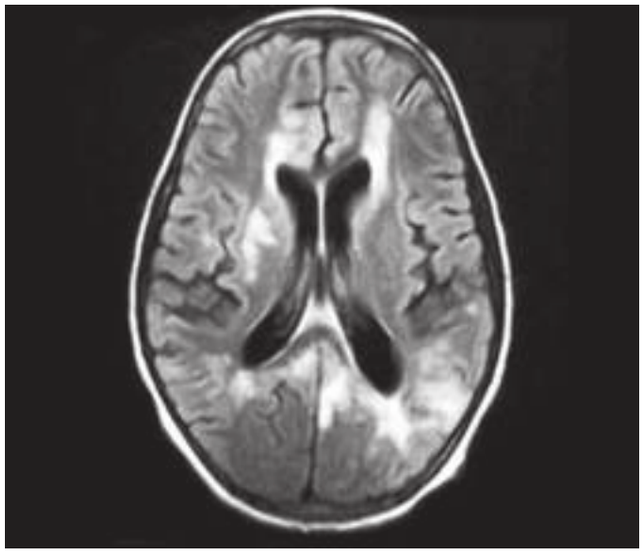

Fig. 18.13: Acute disseminated encephalomyelitis.

Treatment includes supportive management like anticonvulsants along with high-dose IV methylprednisolone (20–30 mg/kg/day × 5 days) followed by PO prednisolone (1–2 mg/kg/day) in tapering doses for 3 month. Other options include IV immunoglobulin (1 gm/kg/day × 2 days) or plasmapheresis. In severe cases, Rituximab may be considered.

Outcome: Most cases recover fully while some are left with residual motor or cognitive deficits. Repeat MRI after 3 months often shows near-complete resolution of radiological changes (except gliosis). Appearance of new clinical signs or MRI lesions beyond 3 months suggests possibility of alternate diagnosis, e.g. multiple sclerosis.

Anti-n-methyl-d-aspartate receptor encephalitis (ANMDAR encephalitis) is the second commonest cause of autoimmune encephalitis after ADEM in children and adolescents.

Etiologically associated with presence of antibodies against NR1 subunit of the NMDA receptor, these cases may be associated with an underlying tumor, e.g. teratoma or *infections,* e.g. Mycoplasma, HSV and influenza.

Clinically, more common in adolescent girls, ANMDAR encephalitis usually presents with progressive behavioral manifestations, e.g. anxiety, agitation, delusion and bizarre behavior, often misdiagnosed as psychiatric disorder. Additional symptoms develop in few days/weeks, including altered sensorium, seizures, dyskinesia, choreoathetoid movements and autonomic instability.

Younger cases often present with complex seizures and movement disorders as psychiatric–behavioral features are missed in them.

Diagnosis rests on presence of NMDAR antibodies in CSF or serum. MRI is abnormal in ~35% cases, usually with bilateral symmetrical densities in temporoparietal

regions on T2 or FLAIR-weighted images. CSF may show moderate lymphocytosis. EEG is abnormal with focal or diffuse slow activity or characteristic *extreme delta brush* pattern. MRI/USG of abdomen, pelvis and testes is required to detect underlying tumors.

While sometimes it is difficult to differentiate it with viral encephalitis, presence of high fever and significant pleocytosis in CSF favours viral etiology.

Management involves removal of tumor (if any), along with immunotherapy with corticosteroids, IVIG, or plasma exchange. Rituximab and cyclophosphamide may be used as second-line alternatives.

Outcome: With mortality rate is <10%, most cases recover substantially, though recovery may be slow, taking 1–2 years. Relapse may occur in ~15% cases.

Rasmussen encephalitis is a rare encephalopathy, usually seen in early school children, characterized by progressive refractory partial seizures, cognitive deterioration and focal deficits with hemiatrophy of cerebral hemisphere. *Etiology* is unknown, may be related to presence of antibodies against the GluR3 subunit of the AMPA receptor, triggered by a viral infection. Immunosuppressive therapy may be useful in some cases, though the definitive treatment is functional hemispherectomy with surgical disconnection of the affected hemisphere.

18.12.5 REYE SYNDROME

Reye syndrome is a clinic-pathological entity, characterized by *generalized loss of mitochondrial functions* and presenting as *acute rapidly progressive encephalopathy with protracted vomiting*. First case of Reye syndrome was probably reported from Jamshedpur, India as *Jamshedpur fever.*

Epidemiology: Once a common cause of acute encephalopathy, the incidence of Reye syndrome has declined in recent years. It is most common between 4 and 12 years of age.

Etiology: *Typical Reye syndrome* is almost always associated with use of aspirin in a mild viral febrile illness, e.g. chickenpox or influenza. However, many *Reye-like illnesses* have been described with mitochondrial dysfunction and similar clinical course, but diverse etiology, e.g. (a) inherited urea-cycle defects, e.g. carbamoyl phosphate synthetase or ornithine carbamyl transferase deficiency, (b) other metabolic disorders, e.g. organic acidemia, and (c) toxin exposure, e.g. aflatoxins.

Pathogenesis of Reye syndrome revolves around the *generalized mitochondrial injury,* leading to decreased activity of hepatic mitochondrial enzymes and consequent impairment in fatty acid, carnitine and ammonia metabolism. *Cerebral edema* is the most important CNS pathology, secondary to hyper-ammonemia, glucopenia and hypoxic/ischemic injury.

TABLE 18.32: Clinical staging of Reye syndrome

Stage	*Features*
I	Lethargy, vomiting, abnormal liver function tests
II	Delirium, hyperventilation, hyperreflexia
III	Light coma, decorticate rigidity, pupillary reflex +
IV	Deep coma, seizures, decerebrate rigidity, fixed-dilated pupils
V	Deep coma, flaccidity, areflexia, apnea, isoelectric EEG

Clinically Reye syndrome presents after 5–7 days of prodromal viral illness with:

- Abrupt onset of intractable vomiting,
- Rapidly progressive delirium, stupor and coma, within few hours of vomiting. Seizures are common but focal signs are often absent.
- Mild/moderate hepatomegaly, though icterus is typically absent till late stages.

Diagnosis is based on a triad of—(a) preceding viral illness/aspirin intake, (b) protracted vomiting, and (c) typical neurological course **(Table 18.32)**, supported by persistent hypoglycemia and absence of icterus.

Laboratory diagnosis is supported with—(a) elevated serum ammonia, (b) protracted hypoglycemia, (c) abnormal LFT including prolonged prothrombin time, (d) normal CSF except elevated pressure, (e) generalized slowing on EEG and (f) microvesicular steatosis without inflammation or necrosis on liver biopsy.

Management of these cases includes:

- Control of cerebral edema with mannitol, steroids and hyperventilation. Phenobarbitone 2.5 mg/kg/dose 8–12 hourly helps to decrease cerebral blood flow, reduce metabolic demands of brain and control seizures.
- General nursing care of a comatose child with constant monitoring.
- Fluid and electrolyte correction/maintenance.
- Treatment of hypoglycemia, acidosis and other complications, e.g. bleeding.

Outcome is good in early cases (grade I/II), though severe cases have high mortality (25–70%) or risk of neurological sequelae, e.g. mental retardation.

18.12.6 CEREBRAL MALARIA

Cerebral malaria-the commonest form of severe falciparum malaria (Ch 10.33), should be considered in differential diagnosis of any case with rapidly progressive febrile encephalopathy, specially without localizing signs.

Pathogenesis of cerebral malaria is multifactorial and probably relates to:

- mechanical vascular injury by parasitized RBCs with increased cytoadherence,
- toxic cellular injury due to immune-mediated release of inflammatory mediators, and

- co-existing metabolic abnormalities, e.g. hypoglycaemia and lactic acidosis.

Cerebral edema is uncommon in cerebral malaria.

Clinically, these cases present with acute onset of:

- High fever with rapidly deepening coma,
- Recurrent generalized seizures in >80% cases,
- Symmetrical motor signs without *focal deficit,*
- Signs of brainstem dysfunction, e.g. decerebrate posture, irregular respiration and gaze abnormalities. Presence of *Pout reflex* is a useful clinical indicator of cerebral malaria.

Diagnosis rests on ***WHO criteria,*** as follows:

- Unarousable coma for >6 hours;
- Confirmed falciparum parasitemia on peripheral smear or rapid diagnostic tests;
- Exclusion of other causes for CNS signs, e.g. febrile seizures, meningitis or hypoglycemia, etc.

CSF is normal except increased pressure and mild lymphocytosis. However, CSF lactate may be elevated (>25 mg/dl indicates poor prognosis).

Treatment of cerebral malaria includes:

- ***Specific therapy:*** Recent data as well as WHO recommendations support the use of IV artesunate over IV quinine in severe malaria, to avoid serious side-effects, e.g. hypoglycemia and hypotension. Further, it takes ~4 hours to achieve adequate quinine levels even after the loading dose.

  Children weighing <20 kg should receive higher dose of artesunate (3 mg/kg/dose) than older ones (2.4 mg/kg/dose) at 12 hourly interval to ensure equivalent exposure to the drug, followed by switch-over to oral ACT as soon as possible for 3 days (*see* **Table 10.56)**.

  In endemic regions, first dose of IV artesunate may be given to suspected cases even before smear confirmation. If IV access is not possible, first dose of artesunate administered rectally before referral has shown to reduce the risk of death in severe malaria.
- ***Supportive therapy***: Coexisting complications, e.g. hypoglycemia and acidosis are major killers in cerebral malaria and all suspected cases of cerebral malaria need intensive care with:
  - *Continuous monitoring* for vital signs, depth of coma and complications, e.g. hypoglycemia, acidosis, dyselectrolytemia and anemia.
  - *Treatment of hypoglycemia* with IV 25% dextrose (2 ml/kg bolus) followed by continuous Dextrose 5–10% infusions.
  - *Correction of fluid/electrolyte imbalance* and metabolic acidosis.
  - *Correction of anemia* with transfusions or preferably partial exchange transfusion, which also helps to reduce parasite load
  - *Control of seizures* with anticonvulsants, e.g. phenobarbitone or diazepam.

Anti-edema measures, e.g. *steroids, mannitol, dextran, etc. have no proven role in treatment of cerebral malaria and are generally contraindicated.* Role of other therapeutic modalities, e.g. pentoxyphylline, deferoxamine, prostacyclines, IV immunoglobulins, hyperbaric oxygen and anti-TNF antibodies is controversial and at best, experimental.

Prognosis: Mortality in untreated cases of cerebral malaria is ~20–30%, with *bad prognostic indicators* being—(i) age <3 years, (ii) deep coma, recurrent seizures and decerebrate rigidity, (iii) absent corneal reflex or retinal hemorrhages, and (iv) co-existing hypoglycemia, severe anemia or lactic acidosis. With adequate treatment, most cases respond dramatically with complete recovery, though late neurological sequelae, e.g. epilepsy, motor deficits and hearing/vision/ speech impairment may develop in <10% cases.

18.12.7 BRAIN ABSCESS

Brain abscess is a serious and focal CNS infection, mainly seen in cerebral cortex, though 20% of them may develop in cerebellum or brain stem.

Etiopathogenesis: Brain abscesses may be caused by: (a) *Infected embolization* from extracranial sites, e.g. infective endocarditis, cyanotic heart diseases, orodental infections, (b) *Direct spread* from neighboring infections, e.g. mastoiditis and otitis, orbital cellulitis, CSF shunts and penetrating head injuries, and rarely as (c) *Residual lesions* following meningitis. Multiple abscesses are seen in ~ 30% cases.

Causative organisms in India generally include: (a) Gram-positive cocci, e.g. *Staph. aureus*, *S. viridans*, *S. pneumoniae*, (b) Anaerobic infections, e.g. bacteroides, (c) Gram-negative bacilli, e.g. *H. influenzae*, Pseudomonas, etc., and (d) Fungal infections in immunocompromised children. Nearly 30% brain abscesses are polymicrobial in etiology.

Clinical features of brain abscess depend on its location, though general features include:

- Constitutional features, e.g. fever and toxemia.
- Signs of raised ICP, e.g. headache, vomiting, papilledema.
- Focal signs, e.g. seizures, ataxia, etc.
- Altered sensorium, e.g. irritability, drowsiness, etc. However, coma is uncommon till terminal stages.

Diagnosis depends on presence of cerebritis or abscess on CT/MRI **(Fig. 18.14)**. Cerebritis appears as a parenchymal low-density lesion, while abscess appears as *ring-enhancing lesion* on contrast CT, with/without mass effect. CSF exam is rarely useful and should be avoided, due to potential risk of brain herniation in presence of raised ICP.

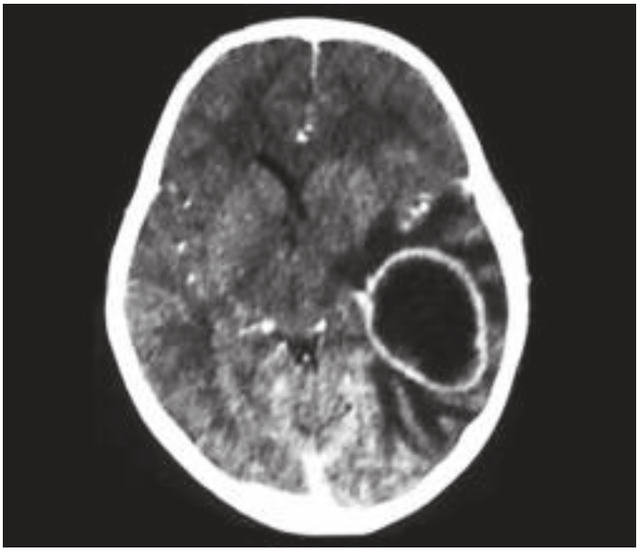

Fig. 18.14: **Brain abscess.**

TABLE 18.33: Intracranial space occupying lesions

- *Infective:*
  - Tuberculoma
  - Brain abscess
  - *Parasitic:* Neurocysticercosis, toxoplasmosis*
- *Neoplastic:* Brain tumors, secondaries
- *Vascular:* Sturge-Weber syndrome, vein of Galen malformation
- *Traumatic:* Subdural hematoma
- *Developmental:* Hydranencephaly, porencephaly

* specially in immuno-compromised host, e.g. HIV.

D/D includes other causes of ICSOL **(Table 18.33)**, though presence of constitutional signs, e.g. high fever with chills and toxemia are highly suggestive of brain abscess in a case with focal neurological deficit.

Management includes IV antibiotic therapy with a third generation cephalosporin and metronidazole for 4–6 weeks. Vancomycin must be added in abscesses following head trauma, surgery or CSF shunts (suspected staphylococcal etiology). Follow-up neuroimaging is necessary to ensure that abscess is decreasing in size.

Surgical drainage is risky due to neurological morbidity, but indicated in cases with—(a) size more than 2.5 cm or evidence of mass-effect, (b) presence of gas or septations in the cavity, (c) suspected fungal etiology, or (d) poor response to antibiotics after 4–6 weeks.

18.12.8 TUBERCULOMA

Tuberculoma is the commonest cause of ICSOL in Indian children, which may be solitary or multiple. While most tuberculomas are supratentorial, infratentorial lesions of cerebellum or brain stem are not uncommon.

Pathogenesis: Tuberculomas denote gradual evolvement of parenchymal *Rich's focus* as chronic inflammatory granuloma, formed during hematogenous spread of pulmonary lesion.

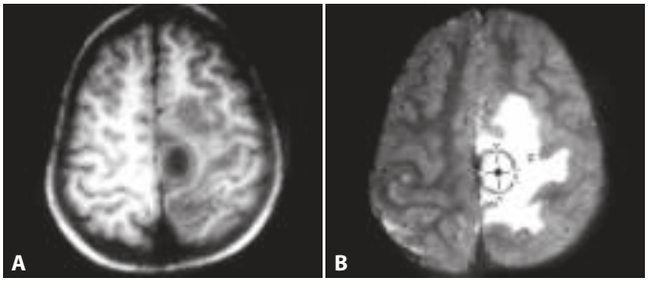

Fig. 18.15A and B: **Tuberculoma. (A) Plain CT; (B) Contrast CT**

Clinically these cases may be asymptomatic for many years or present like other ICSOLs, with recurrent seizures, hydrocephalus with raised ICP or focal neurological deficits.

Diagnosis rests on typical CT/MRI findings, i.e. *solitary or multiple, discrete, ring-enhancing lesions with surrounding cerebral edema and often associated with basal meningitis* **(Fig. 18.15)**. CSF is normal (d/d TBM).

Treatment includes: (a) *specific antitubercular therapy* as per NTEP guidelines, e.g. 2 HRZE + 10 HRE in drug-sensitive cases, (b) *steroids* for first 4–6 weeks, and (c) *prophylactic anticonvulsants*. Specific therapy needs to be modified as per drug/sensitivity/resistance profile after reports. Some cases need CSF shunt surgery.

Outcome depends on the response to specific therapy. Despite successful treatment, these lesions may persist for many months or years and may get calcified.

18.12.9 NEUROCYSTICERCOSIS

Neurocysticercosis (NCC) is the commonest parasitic infection of CNS, caused by the invasive intermediate stage of *T. solium* (pork tapeworm), with formation of asymptomatic or symptomatic cysts in the brain or spinal cord (Ch 10.37.4).

Etiopathogenesis: NCC is caused by ingestion of parasitic eggs, present in soil, water or over the contaminated body of intermediate hosts, e.g. dogs, pigs or cattles (*feco-oral route*). Some of these eggs convert to an invasive form and cross the gut wall to spread hematogenously in different tissues, mainly brain and muscles.

Lodgement of these eggs in tissues produces tiny (2–5 mm) cysts containing single juvenile parasite, i.e. *protoscolex*. These cysts pass through four stages, i.e. vesicular, colloidal vesicular, granular nodular and calcified stage and do not provoke immune response as long as they are viable. However, degeneration of these cysts either in natural course after 5–10 years or after therapy, provokes strong host response and cysts clear up by complete resorption or calcification.

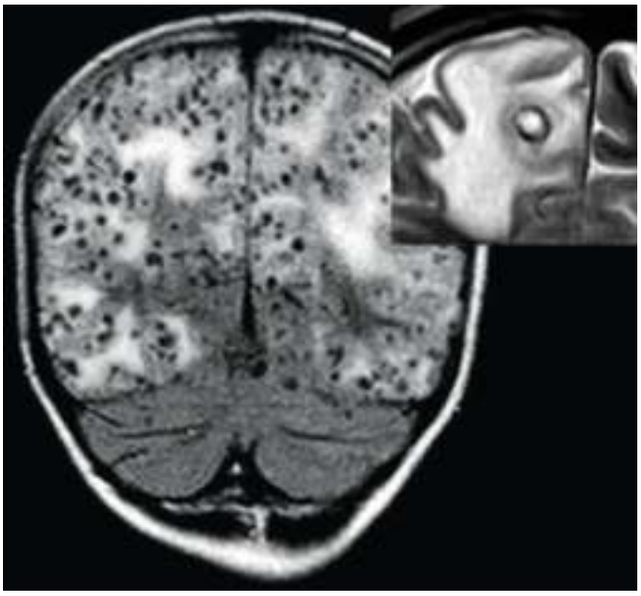

Fig. 18.16: **Neurocysticercosis – Starry sky appearance on CT. Inset: protoscolex on MRI.**

Clinical manifestations depend on the location of cysts as well as host response. Most of these cases remain asymptomatic. Symptomatic cases usually present either as *ICSOL* with recurrent seizures or hydrocephalus, or as *cysticercal encephalitis* with raised ICP.

Rare manifestations include focal motor deficits, signs of meningeal irritation due to meningeal cysts and compressive myelopathy due to spinal cysts. Rarely, cysts may also be present in other tissues, e.g. eyes (impaired vision), skin (palpable under the skin) or in skeletal/heart muscles (myositis/carditis).

Diagnosis: Usually rests on:

- *CT scan* showing single or multiple cysts as ring-enhancing lesions with protoscolex (hyperdense dot within cystic lesion or hole-with-dot appearance), with or without contrast enhancement or calcification. Multiple cysts typically provide *Starry-sky appearance* **(Fig. 18.16)**. Intraventricular cysts may be missed on CT. Calcified lesions appear as hyperattenuating nodule without perilesional edema/ enhancement.
- *MRI with contrast enhancement* is a better imaging tool showing hyperintense lesion in T1 and hypointense in T2 images with *pathognomonic protoscolex. Cysts are Usually <2 cm in size* lesion with well-defined thin rounded walls located near the grey-white matter junction or basal ganglia. Uncommon locations include the posterior fossa, subarachnoid spaces, intraventricular space, and spinal cord.

Though not required for diagnosis, serological ELISA-blot test is sensitive in 90% cases, being false-negative in solitary small or calcified lesions. Stool examination for eggs is positive in <25% cases.

D/D: NCC needs to be differentiated from other causes of ICSOL. Closest d/d includes tuberculoma, based on MRI findings as follows:

- Smaller size of <1–2 cm in NCC *vs* large, confluent lesions in tuberculoma.
- Well-defined thin and rounded cyst walls in NCC *vs* thick, irregular walls in tuberculoma.
- Presence of scoleces within the cysts *vs* hypointense core (T2 images) in tuberculoma.
- Absence of marked perilesional edema, mass-effect or basal meningitis in NCC.
- MR spectroscopy showing multiple amino acid peaks with elevated acetate/succinate ratio in NCC *vs* lipid peak with elevated choline/creatinine and choline/NAA ratio in tuberculoma.

Treatment of NCC includes *anti-cysticercal* therapy, steroids and anticonvulsants as follows:

- ***Specific anti-cysticercal therapy:*** PO Albendazole (15 mg/kg/day q12hr) for 10–14 days is the drug of choice for one or two viable cysts from day 3 onwards of steroid therapy (discussed below) while PO Albendazole along with Praziquantel (PO 50 mg/kg/d) for 10–14 days is recommended for more than two viable cysts.

  Anti-cysticercal therapy is not recommended in acute stage with multiple lesions (>5) or cysticercal encephalitis to avoid worsening of cerebral edema and raised ICP.
- ***Steroids*** (PO prednisolone 2 mg/kg/day q8hr) should be started 2–3 days before specific therapy, as sudden worsening of symptoms due to host response against dying parasites due to antihelminthic drugs is likely in initial phase. Steroids should continue for minimum 2 weeks. IV Dexamethasone (0.6 mg/kg/d) or methylprednisolone (30 mg/kg/d) is preferred in cysticercal encephalitis for 3–5 days, followed by gradual tapering.
- ***Anticonvulsant therapy*** is not required in absence of seizures, while six months of ACT is recommended for single lesions, if lesion resolves on follow-up. Those with persistent lesions or calcifications require minimum 24 months of ACT.
- ***Repeat neuroimaging*** *is recommended after 6 months.* For persistent lesions there are two options – either to repeat the same dose of albendazole or the concurrent administration of albendazole with praziquantel.
- ***Surgical interventions*** for hydrocephalus or removal of cysts blocking CSF pathway is rarely necessary.

18.13 BRAIN TUMORS

Intracranial tumors are the commonest solid tumors and second commonest neoplasms after leukemia in children, accounting for ~15–25% of all neoplasms in different age

TABLE 18.34: Common CNS tumors in childhood

- **Infratentorial tumors**
  - Cerebellar astrocytoma
  - Medulloblastoma
  - Gliomas, e.g. brain-stem glioma, ependymoma
  - Others, e.g. dermoids, teratoma, epidermoids
- **Supratentorial tumors**
  - Craniopharyngioma
  - Cerebral astrocytoma
  - Gliomas, e.g. optic nerve glioma, oligodendroglioma
  - Pineal body tumors: Germ cell tumor, pinealomas
  - Choroid plexus teratoma
- **Secondary leukemic infiltrates** (at any location)

groups. Infratentorial tumors are more common (~2/3rd) except below 2 years of age when supratentorial lesions are equally common.

Classification: As clinical presentation of infratentorial and supratentorial tumors is significantly different, these tumors are best classified according to their location **(Table 18.34)**.

Cerebellar astrocytoma and *craniopharyngioma* are the commonest infratentorial and supratentorial tumors respectively. *Medulloblastoma* is the commonest brain tumor in children <7 years. Gliomas at any site account for ~50% of all brain tumors and ~70% of malignant brain tumors in children.

Etiology: Like other neoplasms, exact etiology is not known but genetic basis exists for some neoplasms, e.g. glioma and meningioma. 25% of optic glioma are associated with neurofibromatosis or tuberous sclerosis. Cranial radiation for leukemia or other metastasis is also known to produce brain tumors.

Pathology: According to the cells of origin, these tumors may be divided as:

- *arising from neuroglial cells*, e.g. astrocytoma, ependymoma and glioblastoma,
- *arising from primitive neuroectodermal cells*, e.g. medulloblastoma and pineoblastoma, and
- *arising from other embryonic remnants*, e.g. craniopharyngioma from Ratke's pouch, dermoids or epidermoids from epithelial cells and chondroma from notochord.

Clinical presentation of brain tumors depends on their location or histological type and includes:

- *Raised intracranial pressure (ICP)* with headache, vomiting and diplopia, is usually the *presenting manifestation in infratentorial lesions*. Important clinical signs include—(i) increasing head size with bulging anterior fontanel and widening of sutures, (ii) positive *Macewan* (crackpot) sign, (iii) papilledema, and (iv) strabismus due to VI nerve palsy (false-localizing sign). Children with extremely raised ICP may develop altered sensorium, coma, bradycardia, hypertension and irregular respiration. Hydrocephalus and raised ICP is a *late sign in supratentorial tumors*, except choroid plexus papillomas (excessive CSF production) and invasive pineal body tumors.
- *Seizures* are common *presenting features in supratentorial lesions*, though these are usually generalized with limited localizing value.
- *Altered behavior and sensorium:* While behavioral abnormalities, e.g. irritability, lethargy and poor academic performance are common and early indicators of all brain tumors, established coma is uncommon, except in terminal stages.
- *Localizing motor signs*, provide valuable diagnostic clues, e.g.
  - *Nystagmus and ataxia* indicates cerebellar tumors. While midline tumors of vermis begin with truncal ataxia, lesions of cerebellar hemisphere produce unilateral ataxia.
  - *Nuchal rigidity and head-tilting* indicates herniation of cerebellar tonsils-a bad prognostic sign and contraindication for lumbar puncture.
  - *Dense hemiplegia* in early stages indicates pontine or medullary tumors. Cranial nerve palsies, e.g. facial and pseudobulbar paralysis is also common in them. Cortical tumors often have non-dense or fine motor deficits.
  - *Cranial nerve involvement* is characteristic in some tumors, e.g. facial palsy in cerebellopontine angle tumors, pseudobulbar palsy in ponto-medullary tumors, vision loss in craniopharyngioma or optic gliomas, and external ophthalmoplegia in pineal body tumors (*Perinaud syndrome*-paralysis of conjugate upward movement of eyes with poorly reactive pupils due to pressure on quadrigeminal plate).
  - *Endocrinal abnormalities*, e.g. short stature, obesity and diabetes insipidus, etc. are common in craniopharyngioma due to pituitary/hypothalamic involvement. Involvement of hypothalamus in optic glioma produces *Diencephalic syndrome of infancy*, i.e. extreme emaciation and anorexia without loss of linear growth or mental changes.

Diagnosis: Neuroimaging with MRI or CT scan is essential to diagnose and delineate intracranial tumors. MRI is better to identify posterior fossa tumors, to define the extent of infiltrating tumors and to diagnose spinal cord metastasis. However, intracranial calcification-commonly seen in craniopharyngioma, may be missed on MRI.

Routine CSF examination has no diagnostic value in brain tumors. Sella turcica tumors, e.g. craniopharyngioma or optic glioma need endocrinal studies before/after surgery.

D/D of brain tumors includes other intracranial space occupying lesions **(Table 18.33)**, specially tuberculoma

TABLE 18.35: D/D supra- *vs* infra-tentorial tumors

Feature	*Supratentorial*	*Infratentorial*
% brain tumors	1/3rd	2/3rd
Age	Younger	Older
Seizures	Common	Rare
Abn. higher functions	Frequent	Rare
Abn. vision/speech	Common	Rare
Focal motor signs	Ill-defined	Common
Raised ICP	Late	Early

Abn: Abnormal, **ICP:** Intracranial pressure

and neurocysticercosis. Clinical presentation and localizing signs in these cases are indistinguishable and CT/MRI is essential to confirm the diagnosis.

Important clinical differences between supratentorial and infratentorial tumors are given in **Table 18.35**.

Management: Control of seizures and raised ICP (with CSF shunt in most cases) is the first priority in these cases. Specific treatment of brain tumors depends on its type and location, as follows:

- *Surgical resection* is the treatment of choice in localized, low-grade neoplastic tumors except in optic nerve glioma and pineal body tumor. Pre/post operative radiotherapy may be useful in large tumors.
- *Chemotherapy* is preferred in optic nerve glioma, pineal body tumor and metastatic tumors from extracranial sites.
- *Radiotherapy* of whole neuraxis is necessary in medulloblastoma and anaplastic ependymoma, along with surgery and chemotherapy in medulloblastoma. *Brachytherapy*, i.e. intracranial implantation of radiation seeds has improved the efficacy and reduced the risk of radiation in treatment of brain tumors.

Outcome: Five-year survival following best therapeutic modalities is *excellent* in cerebellar astrocytoma, medulloblastoma, optic nerve glioma, low-grade astrocytoma and germ cell tumors (70–90%), *good* in ependymoma and craniopharyngioma (50–60%) and *poor* in brain stem glioma and invasive astrocytoma (10–20%). However, post-surgery or irradiation complications are common and include—(a) impairment of intellect, speech and vision, (b) seizures, (c) focal neurological defects, (d) endocrinal abnormalities, and (e) second malignancies.

Some important brain tumors in children are as follows:

Medulloblastoma are midline cerebellar tumors of primitive neuroectodermal origin (PNET), accounting for >40% of posterior fossa tumors in young children, specially boys. Presenting as rapidly growing malignant tumors with cerebellar signs and raised ICP, CSF seeding is present in > 40% cases with poor prognosis.

Cerebellar astrocytoma arise from one of the cerebellar hemispheres and present as low-grade slow-growing tumors with ataxia and other cerebellar signs, which are often localized and fully resectable with favorable prognosis.

Craniopharyngioma are benign cystic tumors, arising from *Rathke pouch* and presenting with growth failure, visual field defects, endocrinal abnormalities, e.g. diabetes insipidus and delayed puberty. X-ray skull may show calcifications and treatment includes cyst aspiration followed by radiotherapy.

Gliomas are commonest CNS tumors across all ages in children, arising from neuronal glial cells. Depending on the site of origin, these tumors are termed as optic nerve glioma, pontine glioma, ependymoma, etc. Juvenile pilocytic astrocytoma is the commonest glioma in children. Some glioma are malignant and not resectable, requiring combination of chemotherapy and radiotherapy for treatment with poor outcome.

18.14 NEUROCUTANEOUS SYNDROMES

Neurocutaneous syndromes (phakomatoses) include a *heterogeneous group of disorders characterized by abnormality of both integuments-skin and central nervous system.* Most of these disorders are familial (except Sturge-Weber syndrome), believed to arise from a defect in differentiation of the primitive ectoderm.

Important neurocutaneous syndromes include *neurofibromatosis, tuberous sclerosis, Sturge-weber disease, Ataxia-telangiectasia, Von-Hippel Lindau disease, Linear nevus syndrome, Hypomelanosis of Ito and Incontinentia pigmenti,* of whom the first four are relatively common and discussed here.

Neurofibromatosis (NF) is the commonest neurocutaneous disorder that represents an abnormality of neural-crest differentiation and migration with two distinct types-more prevalent ***NF_1*** or *Von Recklinghausen disease,* with an estimated incidence of 1:4000, and a rare variant ***NF_2,*** contributing ~10% cases.

Etiology: NF is an autosomal dominant disease though half of the cases are due to spontaneous mutations. Deletion or inactivation of NF gene on chromosome 17 is responsible for NF_1, while NF_2 gene is probably located at chromosome 22.

Clinical manifestations: NF is a progressive neurocutaneous disorders with development of features and complications even beyond childhood. Important clinical indicators of NF include:

a. Oculo-Cutaneous manifestations, e.g.

- *Café-au-lait spots,* i.e. hyperpigmented oval macules over trunk and extremities, sparing the face usually appear in infancy and increase in number and size over time. While also present in normal children,

Fig. 18.17A: **Neurofibromatosis: *Cafe-au-lait* spots.**

Fig. 18.17B: **Neurofibromatosis: Neurofibroma.**

Six or more Café-au-lait spots of >5 mm are hallmark of NF **(Figs. 18.17A and B)**.

- *Axillary or Inguinal freckling*, i.e. multiple hyperpigmented lesions of >2–3 mm in size.
- *Lisch Nodules*, i.e. small-pigmented hamartomas on the iris. Posterior subcapsular lenticular opacities are common in NF_2.
- *Neurofibromas*, i.e. small, rubbery, purplish nodular lesions over skin arising from Schwann cells or nerve sheaths. These lesions usually appear or enlarge during adolescence, though *Plexiform lesions*, i.e. diffuse thickening of nerve trunks in orbital or temporal region may be present at birth.

In addition, *orthopedic complications*, e.g. scoliosis, sphenoidal dysplasia and cortical thinning of long bones, etc. are common in older children.

b. Neurological manifestations are more common in NF_1, though may not be present at the time of diagnosis and include seizures, learning disabilities, speech defects, hydrocephalus/macrocephaly and transient ischemic attacks with hemiparesis.

c. Other neoplastic lesions, e.g. optic glioma, acoustic glioma, meningioma, pheochromocytoma, leukaemia and Wilms tumor. Optic gliomas with/without vision defects are more common in NF_1, while bilateral acoustic neuromas are distinctive features of NF_2.

Diagnosis is largely clinical, as follows:

- ***Diagnostic criteria for NF_1 (2021)*** include presence of *any two* of the following (or *any one* feature with NF_1 in either parent):
  - Six or more Café-au-lait spots >5 mm in greatest diameter,
  - Axillary or inguinal freckling,
  - Two or more Lisch Nodules or choroid abnormalities
  - Two or more Neurofibromas of any type or one plexiform neurofibroma,
  - Distinctive osseous lesions, e.g. sphenoid dysplasia, cortical thinning of long bones, etc.
  - Optic nerve glioma with/without vision defects,
  - Heterozygous pathogenic variant in >50% of normal tissue, e.g. WBCs.
- ***Diagnostic criteria for NF_2*** include:
  - Bilateral acoustic neuroma on CT/MRI *or*
  - Family history of NF_2 in first-degree relatives with:
    - Unilateral acoustic neuroma, *or*
    - Any two of the following—(i) neurofibroma, meningioma, (iii) glioma, (iv) Schwannoma *or* (v) posterior subcapsular lenticular opacities.

No investigations are needed except neuroimaging and EEG in cases with neurological features.

Prenatal diagnosis by fetal DNA analysis is indicated in cases with family history.

Treatment is non-specific, except follow-up for detection of complications and tumors. Neurofibromas of peripheral nerves are indolent and largely cosmetic lesions and need not be removed unless compressing the nerves, or subjected to repeated irritation/trauma or develop malignant changes. Some plexiform neuromas may be removed for cosmetic purpose.

Tuberous sclerosis (TS) is a heterogeneous disease with wide clinical spectrum affecting many organs, e.g. skin, brain, heart, kidney, eyes, lungs and bone.

Etiologically, it is inherited as autosomal dominant disease (with two identified gene loci-TSC1 at chr9q34, and TSC2 at chr16p13), though ~ 50% cases are sporadic mutations. TSC1 gene encodes a protein *hamartin*, while TSC2 encodes another protein *tuberin*.

Pathologically, typical brain lesions consist of *subependymal tubers, which* undergo calcification and project into the ventricular cavity, producing *candle-dripping* appearance.

Fig. 18.18A: **Tuberous sclerosis: Adenoma sebaceum.**

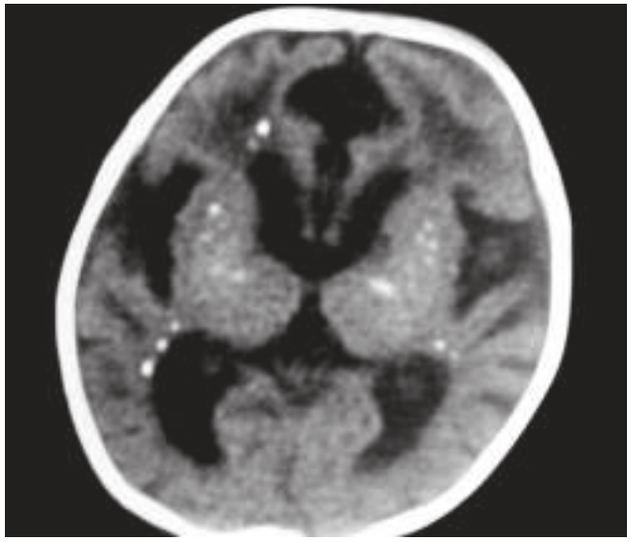

Fig. 18.18B: **Tuberous sclerosis: Dripping candle appearance on CT scan.**

Clinical spectrum is extremely heterogeneous, ranging from asymptomatic disease except few cutaneous markers to severe intellectual disability and refractory seizures in same family.

Intractable infantile spasms may be earliest indicator of TS in first year of life, though most cases present beyond infancy with:

- ***Cutaneous lesions:***
  - *Ash-leaf macules,* i.e. characteristic hypopigmented lesions over trunk and limbs are earliest cutaneous markers, present since birth in 90% cases and best visualized by Wood's ultraviolet lamp.
  - *Adenoma Sebaceum,* i.e. tiny red or pink nodules over face mainly in perinasal region, generally seen from 4–6 years onwards, which may coalesce later to give a fleshy appearance **(Fig. 18.18A)**.
  - *Shagreen Patch,* i.e. rough, raised lesions with orange peel consistency, usually in lumbosacral region.
  - *Periungual fibromas* with fleshy nodules around nails, developing during adolescence.
- ***Neurological manifestations:***
  - *Recurrent seizures*, as infantile spasms in infancy or generalized seizures in later childhood.
  - *Intellectual disability,* more severe in cases with early presentation and infantile spasms.
  - *Hydrocephalus*, due to obstruction of CSF flow at foramen of Monro by tubers.
  - Presence of *calcified tubers* in periventricular area, from 3–4 years onwards on MRI.
  - *Retinal Lesions*, e.g. mulberry tumors or phakoma (flat-gray lesions) over or around optic disc.
- ***Extra-CNS tumors***, e.g. rhabdomyoma of the heart, renal tumors and angiomyolipomas in lung. Rhabdomyomas are commonest tumors in TS, seen in ~50% cases. While these tumors may be detected *in utero* on fetal echocardiography and lead to CCF and arrhythmia in infancy, most of them resolve spontaneously with age.

Diagnosis: Apart from cutaneous markers, confirmation of TS requires *demonstration of one or more calcified periventricular tubers* on CT/MRI, often giving a *Dripping Candle appearance* **(Fig. 18.18B)**.

Since calcified tubers may not be visible on CT scan before 3–4 year of age, MRI is more useful for early detection of uncalcified tubers and alterations in cortical cyto-architectonics. EEG may reveal *hypsarrhythmia* in cases with infantile spasms.

Diagnostic criteria of TS include *presence of any two of eleven major criteria or any one major and two of the six minor criteria.*

- *Major criteria* include-Hypomelanotic macules >3–5 mm. Three or more angiofibroma, Two or more Ungual fibroma, Shagreen patch, Multiple renal hamartoma, Cortical dysplasia, Subependymal nodules, Subependymal giant cell astrocytoma, Cardiac rhabdomyoma, Lymphangioleiomyomatosis and two or more Angiomyolipoma.
- *Minor criteria* include Confetti skin lesions, three or more dental enamel pits, two or more intraoral fibroma, retinal achromic patch, multiple renal cysts and non-renal hamartomas.

Treatment of TS includes—(a) control of seizures by anti-epileptic drugs, (b) management of hydrocephalus with shunt surgery, (c) follow-up for early detection of renal, cardiac or pulmonary lesions and (d) genetic counseling. TS associated Infantile spasms respond better to vigabatrin than ACTH.

Everolimus (MTOR inhibitor) has been approved from TS with refractory epilepsy, subependymal giant cell astrocytoma and renal angiomyolipoma.

Fig. 18.19A: **Sturge-Weber syndrome: Facial hemangioma.**

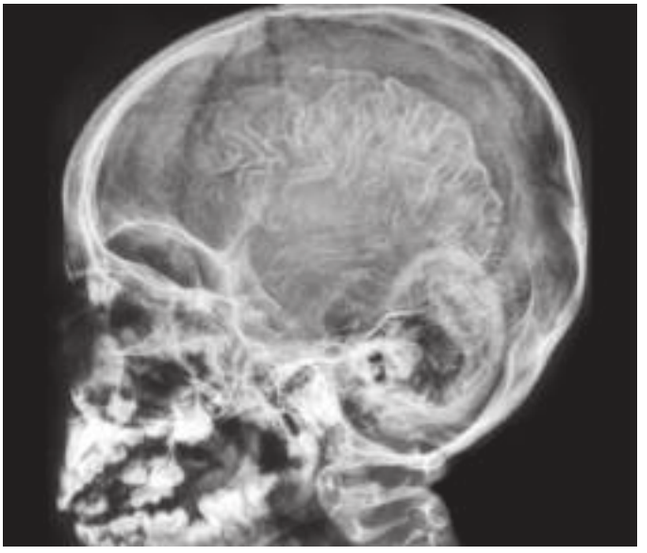

Fig. 18.19B: **Sturge-Weber syndrome: Tram-track appearance.**

Rarely, subependymal nodules may increase in size and turn malignant and periodic MRI every 2–3 years is recommended to monitor size of these nodules.

Sturge-Weber syndrome (SWS) is characterized by a combination of *facial and intracranial hemangiomatosis*, presenting with recurrent seizures, focal motor deficits and intracranial calcifications.

Etiology: SWS is not hereditary, but related to somatic mutations in GNAQ gene. It is thought to result from anomalous development of primordial cephalic vascular bed during early stages of vascularization.

Clinical features include:

- *Facial nevus* (Port-wine stain) since birth, mainly over upper face and eyelid **(Fig. 18.19A)**.
- *Neurological features*, e.g. contralateral focal seizures due to intracranial hemangioma, with/without progressive hemiparesis, mental retardation or learning disabilities.
- *Ocular features*, e.g. Buphthalmos and glaucoma in ipsilateral eye.

On ***Roach scale***, SWS is classified as—(a) Type I with facial and intracranial angiomas, (b) Type II with Facial angioma without CNS involvement and (c) Type III with Intracranial angiomas without facial involvement.

Diagnosis depends on combination of facial and neurological features and presence of typical intracranial calcifications on skull X-rays termed as *Rail-road or Tram-track appearance* **(Fig 18.19B)**. CT scan may reveal calcification and ipsilateral cortical atrophy with ventricular dilatation.

Treatment includes—(a) control of seizures, (b) surgical lobectomy/hemispherectomy in refractory seizures, (c) treatment of facial nevus with laser therapy, and (d) regular monitoring of intraocular tension for glaucoma.

Ataxia telangiectasia, an autosomal recessive disorder due to mutation in ATM gene on chromosome 11q, is characterized with slowly progressive cerebellar ataxia from 1–3 years of age and telangiectatic vascular lesions over skin and conjunctiva. Choreoathetosis and ocual apraxia is common.

Common associated abnormalities include IgA deficiency leading to recurrent sinopulmonary infections and lymphoreticular malignancies.

18.15 NEURODEGENERATIVE DISORDERS

Neurodegenerative disorders (NDD) is a collective term to denote broad spectrum of heterogeneous disorders, all characterized by *Progressive deterioration or regression of neurological functions,* e.g. intellect, speech, vision, hearing and locomotion, with or without other manifestations, e.g. seizures.

Classification: NDD may be classified according to etiology, age of onset and biochemical defects, though most useful is the classification based on primary site of lesion that helps in clinical diagnosis **(Table 18.36)**.

Etiologically, these disorders may be *inherited* due to genetic biochemical defects or *acquired* following chronic viral infections, toxic encephalopathies and idiopathic brain injury.

Metachromatic leukodystrophy is the commonest hereditary NDD in Indian children, while subacute sclerosing panencephalitis (SSPE) due to slow measles virus infection is the commonest acquired NDD.

Almost *all hereditary NDDs are autosomal recessive, except x-linked recessive adrenoleukodystrophy and Menkey (kinky hair) disease.*

Pathologically, NDDs include *storage* and *non-storage* disorders. Storage disorders are characterized by

TABLE 18.36: Common neurodegenerative disorders

- **Gray matter degeneration**
  - ***Storage disorders*** *(Sphingolipidoses):*
    GM1 gangliosidoses (Infantile and juvenile)
    GM2 gangliosidoses (Tay-Sachs disease, Sandhoff disease)
    Neuronal ceroid lipofuscinoses
    Others: Gaucher disease, Niemann-Pick disease
  - ***Non-storage disorders***
    Subacute sclerosing panencephalitis (SSPE)
    Menkes Kinky hair disease
- **White matter degeneration**
  - ***Leukodystrophies***
    Metachromatic Leukodystrophies
    Adrenoleukodystrophies
  - ***Demyelinating diseases***
    Multiple sclerosis (Neuromyelitis optica)
    Schilder disease
- **Spinocerebellar degeneration**
  Friedreich's ataxia
  Ataxia telangiectasia
  Abetalipoproteinemia
  Refsum disease
- **Basal ganglia degeneration**
  Wilson disease
  Huntington chorea
  Hallervorden-Spatz disease
  Dystonia musculum deformans

excessive intracellular storage of either normal or abnormal lipid component of cell membrane, due to some inherited enzymatic defect in their catabolism. Macrocephaly is an important feature of storage disorders. Non-storage disorders may be hereditary or acquired, associated with either poor myelin formation or subsequent demyelination.

Clinical manifestations: *Early development is characteristically normal in NDDs, till the onset of disease.* Age of onset and early clinical manifestations vary according to the site and type of lesion, though end-stage clinical picture is often similar with crippling loss of intellect, voluntary motor activity and severe impairment of vision, hearing and speech. Among hereditary defects, children with complete absence or severe deficiency of causative enzyme present at birth/infancy, while those with moderate or mild deficiencies present as juvenile or adult variants.

Gray matter disorders generally begin with regression of mental milestones, intellectual dysfunction, seizures and visual/hearing impairment. Motor dysfunction is a late feature in these disorders.

White matter disorders usually present with early pyramidal tract signs, e.g. regression of motor milestones, spasticity or hypotonia, gait disturbances and feeding difficulties due to pseudobulbar palsy. Intellectual impairment and seizures are usually late manifestations in these conditions.

Diagnosis requires—(a) precise history and clinical examination including fundus examination specially for cherry-red spot, (b) neuroimaging with MRI (CT scan is not very useful), and (c) specific biochemical tests to identify enzyme deficiency or storage substance.

Molecular studies on leukocytes or skin fibroblasts to identify genetic defect in index case and carrier-detection are essential for genetic counseling in hereditary NDDs and prenatal diagnosis is possible for many diseases.

Management of NDDs is largely supportive and most patients succumb to illness after variable period of time. Some important NDDs are discussed as follows:

Subacute sclerosing panencephalitis (SSPE) or *Dawson encephalitis* is the commonest acquired NDD in India, due to the slow virus infection of CNS after many years of measles disease or vaccination.

Incidence of SSPE is estimated to be ~8 per million clinical cases and <1 per million vaccinations of measles.

Clinically, these cases present by late childhood, after 4–5 years of measles attack, with:

- *Personality changes*, e.g. emotional instability and deterioration in school performance (earliest features).
- *Myoclonic seizures* followed by tonic-clonic seizures, hypertonia, choreoathetoid movements and developmental regression with decerebrate posturing.
- *Ophthalmic signs*, e.g. papilledema, optic atrophy, chorioretinitis or macular pigmentation in late stages of most cases.

Diagnosis is established by—(a) past history of measles ~4–5 years back, (b) typical clinical progression, (c) presence of measles antibodies in CSF, and (d) characteristic EEG with *repeated bursts of high voltage slow wave complexes.* Post-mortem brain biopsy may confirm the diagnosis on histology and viral culture.

Management is supportive and antiviral therapy is not effective. Some drugs, e.g. intraventricular interferon -2B and isoprinosine have been tried with unproven benefit. Most cases die within 2–3 years of onset.

Metachromatic leukodystrophy (MLD) is the commonest hereditary NDD in India, characterized by *Arylsulfatase-A deficiency*, leading to accumulation of *cerbroside sulfate* in the myelin sheaths.

Classic MLD presents at 1–2 years of age, with gait disturbances, inability to walk/stand, hypotonia and hyporeflexia followed by gradual intellectual impairment, dysarthria and loss of vision (optic atrophy). MRI reveals diffuse symmetrical hyperintensities in the deep white matter, while sparing the subcortical U-fibres. Most cases die by 5–6 years due to aspiration Bone marrow transplant is only promising therapy for MLD, still in experimental stage.

Other variants present similarly but at a later age, i.e. 5–10 years (***Juvenile MLD***) or adults (***Adult MLD***).

Adrenoleukodystrophies (ALD) include a group of NDDs associated with adrenal cortical deficiency. ***Classic ALD*** (X-linked), presents between 5–15 years of age with academic deterioration, seizures, pyramidal tract signs and pseudobulbar palsy. Presence of *abnormal skin pigmentation (adrenal insufficiency) is an important indicator* of ALD. However, correction of adrenal insufficiency doesn't affect the course of disease and death is common within 8–10 years of onset. MRI brain demonstrates predominant parieto-occipital white matter involvement with contrast enhancement. Diagnosis is supported by presence of high levels of *very long chain fatty acids* in serum. Bone marrow transplant may prevent further worsening of neurological status in ALDs, to some extent.

Other variants include ***Neonatal ALD***, presenting in newborns or early infancy with severe hypotonia, psychomotor retardation, optic atrophy and seizures; and ***Adrenomyeloneuropathy*** in adults beyond 3–4th decade of life.

Krabbe disease (KD) is a rare autosomal recessive (*GALC* gene) disease with severe myelin loss and the presence of globoid bodies in white matter due to deficiency of a lysosomal enzyme *galactocerebroside* β-*galactosidase*.

Clinically most cases present in early infancy with excessive cry, hyperpyrexia, vomiting and difficulty feeding followed by development of seizures, rigidity, blindness (optic atrophy) and deafness. Most patients die by 2 years of age. *Late-onset KD* may present in older children or adolescents with ataxia, progressive rigidity and blindness, often confused with adrenoleukodystrophy.

MRI and MR spectroscopy clinch the diagnosis and stem-cell transplant may be useful in early stages. Prenatal diagnosis is possible by enzyme assay in chorionic villi/amniotic fluid cells.

Gangliosidoses are multiple autosomal recessive disorders of ganglioside catabolism (a normal lipid in cell membranes) due to various enzyme deficiencies, leading to its accumulation within the neuronal cells.

Presence of *cherry-red spot over macula* **(Fig. 27.1D)** *is highly suggestive of all gangliosidoses*, except in juvenile GM_2 gangliosidsis. Important gangliosidoses include:

GM_1 gangliosidoses (β-glucosidase deficiency) has three variants:

a. ***Infantile disease***, presenting since birth with marked developmental retardation, seizures, coarse features and hepatosplenomegaly;
b. ***Juvenile disease***, presenting at ~1 year with progressive ataxia, spasticity and seizures, but *without* coarse features or hepatosplenomegaly.
c. ***Adult disease*** with further late presentation.

GM_2 gangliosidoses (Hexoaminidase deficiency) also has three variants:

a. ***Tay-Sach disease*** (Hex A deficiency) is more common in Jews and presents at 5–6 months of age with hyperacusis (exaggerated startle response), developmental regression, spasticity, seizures and blindness;
b. ***Sandhoff disease*** (Hex A and B deficiency) with similar presentation but with splenomegaly;
c. ***Juvenile or adult*** GM_2 gangliosidoses, presenting in mid-childhood or later, with progressive ataxia and spasticity. Visual and intellectual functions are relatively preserved and *cherry-red spot is uncommon.*

Neuronal ceroid lipofuscinoses (NCL) are commonest NDDs in western children, characterized by storage of an autofluorescent substance in neurons and other tissues.

Of three variants, all autosomal recessive, commonest is ***late infantile NCL***, presenting at 2–4 years with myoclonic seizures, progressive dementia, ataxia and loss of visual acuity. Brown/black retinal pigmentation with optic atrophy and abnormal visual evoked potential studies are typical.

Other variants include ***early infantile NCL***, presenting by one year of age and ***juvenile NCL***, with onset at 5–10 years.

Multiple sclerosis is a common chronic remitting NDD in adults with multiple white lesions in brain due to inflammatory demyelination and axonal degeneration. Less than 1% of these cases present in childhood.

Menkes (kinky hair) disease, an X-linked recessive disorder of copper metabolism, presents with myoclonic seizures in early infancy, failure to thrive, severe mental retardation, optic atrophy and typical sparse, colorless and brittle hair. Most cases die by 2–3 years. Serum copper and ceruloplasmin levels are consistently low. Parenteral copper histidine administration either intravenously or subcutaneously may prevent neurological deterioration, if started in neonatal period.

Rett syndrome, due to mutation in MECP2 gene is most commonly seen in girls and present with developmental regression from 1–2 years of age, followed by development of typical autistic behavior, peculiar sighing respiration with intermittent apnea and Loss of purposeful hand movements with repetitive hand-wringing movements (hallmark features). Seizures are common. Most cases survive till late adolescence.

Friedreich ataxia, an autosomal recessive disorder due to expansion of a GAA trinucleotide repeat region, is the commonest NDD with spinocerebellar degeneration, presenting in late childhood or adolescence with:

- Posterior spinal column involvement with loss of position and vibration sense,
- Pyramidal tract involvement with spasticity and extensor planter response,

- Spinocerebellar tract involvement with ataxia, nystagmus and dysarthria,
- Peripheral neuropathy with areflexia, and
- Coexisting skeletal deformities, e.g. *Pes cavus.*

Extensor planter response (pyramidal tract lesion) with absent ankle jerk (peripheral neuropathy) is a useful indicator of Friedreich ataxia.

Hallevorden Spatz disease, a rare recessive NDD with iron accumulation in the brain, presents in childhood with progressive dystonia, rigidity, choreoathetosis and dysarthria. Mental deterioration and spasticity develops in adolescence with death in early adulthood. Neuropathology reveals accumulation of iron-containing pigment in globus pallidus and substantia nigra, which may be visible on MRI as *eye-of the-tiger sign* in globus pallidus.

Dystonia musculorum deformans is a rare autosomal dominant disorder, more common in Ashkenzi Jews.

Clinical manifestations generally begin in mid-childhood with intermittent attacks of unilateral leg dystonia with abnormal gait (*tip-toe* walking), aggravated by stress. Gradually, the attacks become more persistent, involving all extremities, face and trunk, with severe postural deformities and feeding/speech difficulties.

Diagnosis is clinical and severe cases may benefit from large doses of trihexyphenidyl, carbamazepine, levodopa or diazepam.

Some other important NDDs – *ataxia telaniectasia, Wilson disease and Huntignton chorea,* have been discussed elsewhere in Ch 15.8, 18.9 and 18.14 respectively.

18.16 SPINAL CORD DISORDERS

Spinal cord disorders in children may be divided into infective, developmental, traumatic, neoplastic and degenerative disorders. Poliomyelitis is the commonest spinal cord disorder in Indian children involving anterior horn cells, discussed in Chapter 10.21. Other common disorders are as follows:

18.16.1 ACUTE TRANSVERSE MYELITIS

Acute transverse myelitis is characterized by abrupt onset of progressive weakness and sensory disturbances in lower extremities following *viral infections*, e.g. EBV, HSV, Influenza, rubella, varicella, etc.

Etiologically, Transverse myelitis is thought to be the result of direct viral invasion of the spinal cord, or more likely, an immunological reaction to viral infections.

Clinically, these cases present with:

- *Prodromal features,* e.g. fever, nuchal rigidity, low backache and parasthesia following a viral infection.
- *Acute flaccid parelysis of lower limbs with loss of external senses,* e.g. pain and temperature but preservation of proprioceptive senses, e.g. position and vibration. Sensory involvement has a characteristic identifiable spinal level. Bladder involvement is common.
- *Changing course from flaccid to spastic lesions,* over next few days with appearance of upper motor neuron signs.

Diagnosis is mainly clinical, based on sensory level and the change from flaccid to spastic paralysis. CSF is normal or shows mild elevation of proteins and cells. MRI reveals *mild to moderate fusiform swelling* in the affected region. Early cases must be differentiated from other causes of acute flaccid paralysis.

Management is largely supportive including general nursing care, treatment of complications and physiotherapy. Spontaneous recovery occurs in ~ 60% cases within few months with residual deficit. High-dose steroids, e.g. methylprednisolone may be beneficial in initial stages of the disease. other therapeutic approaches include IV immunoglobulin, plasmapherersis or Rituximab in refractory cases.

18.16.2 SPINAL CORD INJURIES

Acute spinal cord injuries in children range from mild concussion to contusions, laceration and complete transaction and may occur even without vertebral fractures. *Spinal cord injury without radiographic vertebral abnormality* (SCIWORA) is more common in children than adults.

Common causes of spinal cord injury in children include breech delivery, vehicular/sports accidents, physical abuse (Shaken baby syndrome) or vertebral pathologies as seen in Down syndrome (atlanto-axial joint instability), hemolytic anemia (extramedullary erythropoiesis), Pott's spine and tetanus (during spasms).

Clinical manifestations depend on the site and extent of injury. Complete transaction presents with a stage of spinal shock with acute flaccid paralysis and definite level of sensory loss below the lesion during first 24–48 hours.

This stage of spinal shock may persist from few hours to few weeks, followed by gradual development of spasticity and other upper motor neuron signs. Bladder/bowel dysfunction is common. High cervical (C_{1-2}) injury may cause sudden death due to respiratory arrest.

Diagnosis rests on spinal MRI. Periodic cervical X-rays are advised in high-risk cases, e.g. Down syndrome, to detect atlantoaxial instability (>4.5 mm distance between odontoid process of axis and anterior arch of atlas).

Management of spinal cord injury includes: (a) stabilization and immobilization of spine during resuscitation and transport, (b) high-dose IV methylprednisolone (30 mg/kg Loading followed by 5.4 mg/kg/hr), (c) diagnostic confirmation by MRI, and (d) definitive orthopedic interventions, as required.

18.16.3 SPINAL CORD MALFORMATIONS

Apart from major neural tube defects, e.g. meningomyelocele (Chapter 18.9.1), other important malformations of spinal cord, which usually present in later life, are as follows:

Syringomyelia, i.e. *cystic dilatation of the central canal,* may be congenital *or* acquired after cord tumors, trauma or infections. Congenital syrinomyelia is frequently associated with Arnold-Chiari malformation and communicates with CSF pathway, while acquired lesions are generally non-communicating. *Syringobulbia* is the similar lesion in medulla.

Clinically, most cases present beyond childhood due to slowly progressive dilatation of central canal with – (a) *dissociate anesthesia*, i.e. loss of pain and temperature sense without light touch, due to spinothalamic tract involvement and (b) *spastic motor lesions* below the lesion due to compression of corticospinal tracts.

Diagnosis rests on MRI or Metrizamide CT scan and management includes surgical decompression of cystic cavity, depending on the site and etiology.

Diastematomyelia is a neural tube defect due to vertical division of the spinal cord into two halves by a fibrocartilagenous or bony projection from the posterior vertebral body, commonly at L_{1-3} levels. These cases may be asymptomatic or present with low backache and progressive sensory/motor lesions in lower limbs.

Diagnosis rests on CT/MRI and symptomatic cases need surgical intervention with excision of bony spur/septum and lysis of adhesions.

Tethered cord syndrome: *In utero*, spinal cord occupies the entire vertebral canal, but postnatal differential growth leads to regression of distal end, i.e. *conus medullaris* till L_1 level. Normally, this conus is attached to coccyx with a slender thread like *filum terminale*.

A tethered cord denotes persistence of a thick rope like filum terminale that anchors the conus at or below L_2, leading to abnormal traction and vascular compromise during spinal bending movements.

Clinically, these cases are asymptomatic or present at any age with diffuse pains and muscle wasting in lower limbs, bladder/bowel dysfunction with overflow incontinence and progressive scoliosis. Midline skin lesions, e.g. pits or tuft of hair, are common over spine.

Diagnosis may be confirmed on MRI and treatment involves surgical transaction of *filum terminale*.

18.16.4 SPINAL CORD TUMORS

Spinal cord tumors account for ~20% of neuraxial tumors and are classified according to their location as—(a) intramedullary, (b) extramedullary, and (c) extradural tumors.

TABLE 18.37: D/D intra *vs* extra-medullary spinal tumors

Feature	*IML*	*EML*
Back pain	Rare	Presenting
Root pains	Rare	Common
Paresthesia	Below the lesion	Segmental
LMN signs	At the lesion	Segmental
UMN signs	Below the lesion	Uncommon
Sphincters	Early	Late
MRI	Fusiform swelling	Circular indentation

IML: Intramedullary, **EML:** Extramedullary

Intramedullary tumors commonly develop in cervical region as slow-growing astrocytoma, presenting with:
- LMN signs at the site of lesion,
- UMN signs and sensory loss below the lesion,
- Spastic bladder involvement,
- Fusiform swelling of cord on MRI.

Extramedullary tumors are usually benign, arising from neural crest tissue, e.g. neurofibroma and presenting with:
- Severe back pain/stiffness (*Tripod posture*),
- Root pains,
- Segmental weakness,
- Circular indentation of cord on MRI (neurofibroma)

Extradural tumors are usually metastatic, e.g. neuroblastoma, lymphoma, etc., which present with:
- Flaccid paraplegia,
- Urinary retention and patulous anus,
- Raised ICP with elevated CSF proteins due to obstruction of spinal CSF flow by tumor (Froin syndrome),
- *Brown-Séquard syndrome*, i.e. ipsilateral weakness, spasticity, ataxia with contralateral loss of pain and temperature sense in some cases.
- Spinal block on MRI.

Diagnosis of spinal tumors rest on MRI, though plain spinal skiagrams may show variable abnormalities, e.g. widening of interpediculate distance, destruction of vertebral bodies and widening of vertebral foramen. Important clinical differences between intramedullary and extramedullary tumors are shown in **Table 18.37**.

Treatment: Surgery is the treatment of choice in all cases, with best results for extradural tumors.

18.17 PARAPLEGIA

The term paraplegia or paraparesis denotes *complete or partial weakness of both lower limbs, respectively.* Clinically, it may be further classified according to duration (acute or subacute) and type of lesion (spastic or flaccid).

Etiology of paraplegia is best classified according to the site of lesion **(Table 18.38)**.

TABLE 18.38: Causes of paraplegia in childhood

Spastic paraplegia
- **Cerebral (rare)**
  Sagittal sinus thrombosis
  Cerebral palsy
- **Spinal cord lesions**
  Inflammatory: Acute transverse myelitis
  Compressive: Pott's spine, extradural abscess
  Tumors: Spinal tumors, secondaries
  Traumatic: Spinal cut-injury section, hematomyelia
  Vascular: Arteriovenous malformations
  Anatomical: Syringomyelia, diastematomyelia
  Degenerative: Familial, post-ARV vaccination
  Toxic: Lathyrism, subacute combined degeneration

Flaccid paraplegia
- **Spinal shock**
- **Anterior horn cell disease:** Poliomyelitis, SMA
- **Vertebral deformities** *(Nerve compression)*
  Kyphoscoliosis, lordosis
  Collapse of vertebral body - traumatic, pathological
- **Peripheral neuropathies**
  Guillain-Barré syndrome
  Others *(Ch. 18.18.2)*
- **Myopathies**
  Duchenne muscular dystrophy
  Others *(Ch. 18.18.4)*
- **Miscellaneous**
  Autonomic neuropathy: (Riley-Day syndrome)
  Hysteria

SMA: Spinal muscular atrophy

- *Spastic paraplegia* is usually seen below the level of spinal cord lesions, commonest being spinal tuberculosis (Pott's spine), spinal injuries and neural tube defects.
- *Flaccid paraplegia* usually indicates anterior horn cell disease, e.g. poliomyelitis, acute transverse myelitis or neuropathies, e.g. Guillain-Barré Syndrome (GBS) and traumatic neuritis.

Diagnostic approach in paraplegia aims to—(a) localize the site of lesion, and (b) identify probable etiology. Important steps in evaluation include:

Step I. Whether paraplegia is spastic or flaccid?
Spastic paraplegia is characterized by UMN signs, e.g. spasticity, hyperreflexia and extensor planter response, usually due to thoracic or lumbar cord lesions. Cervical cord lesions present with quadriparesis.

Flaccid paraplegia with LMN signs, i.e. hypotonia, hyporeflexia and flexor planter response, is usually seen in *neuromuscular disorders* or in *spinal shock* (first few days after acute spinal injury, before signs of UMN lesions appear).

Acute, symmetrical and *ascending* muscle weakness indicates GBS, while muscle weakness is typically acute and asymmetrical.

Atrophy or pseudohypertrophy of muscles indicates neuropathy or myopathy, respectively. Muscle weakness is mainly proximal in myopathies and distal in neuropathies.

Step II. Whether sensory involvement is present?
Presence and level of sensory involvement, e.g. anesthesia or paresthesia indicates site of spinal cord injury* in spastic paraplegia and peripheral neuropathy in flaccid paraplegia. Spinal cord lesions are usually associated with *anesthesia below* the level and *paresthesia at* the level. Presence of root pains indicates nerve compression (compressive myelopathy), as seen in extramedullary tumors or Pott's spine.

*While sensory examination assists to identify the spinal segment of lesion, these spinal segments do not correspond to vertebral level. For identification of vertebral lesion *subtract 1* from cervical spine levels (e.g. C_8 = 7th cervical vertebrae), *subtract 2* from T_{1-8} lesions (T_8 = 6th thoracic vertebrae) and *subtract 3* for T_{9-12} lesions (T_{12} = 9th thoracic vertebrae). Lumbar spinal segments L_{1-2}, L_{3-4} L_5 correspond with 10th,11th and 12th thoracic vertebrae. Sacrococcygeal spinal segments originate from 1st lumbar vertebrae.

Step III. Whether bladder is involved?
Urinary bladder is frequently involved in paraplegia. *Spastic bladder*, i.e. low capacity, contracted bladder with frequent reflex emptying and loss of voluntary control indicate spinal lesions above the level of L_{1-2}. Bladder in LMN lesions or spinal shock may be either distended with over-flow incontinence (*atonic bladder*) or empty reflexly at regular intervals without voluntary control (*autonomic or autonomous bladder*).

Step IV. What is the onset, duration and progression of weakness?
Acute paraplegia of a few minutes or hours duration is mainly vascular or traumatic; while more *insidious lesions* developing over a few days may be due to transverse myelitis, infective spinal lesions, poliomyelitis or Guillain-Barre syndrome.

Paraplegia, evolving over a few weeks or months indicates intraspinal space occupying lesions (tumors, abscesses, hematoma) or compressive myelopathy, syringomyelia and degenerative disorders of spinal cord. Peripheral neuropathies and myopathies, involving lower limbs also present as slowly developing paraparesis.

Step V. Paraplegia is in flexion or extension?
Paraplegia in flexion is characterized by predominant flexor weakness and spasticity in lower limbs and indicates generalized or complete involvement of spinal pyramidal tracts. *Paraplegia in extension* indicates incomplete pyramidal tract lesions.

Step VI. Search for spinal deformities, e.g. obvious neural tube defects, tuft of hair/dimple or sinus (Spina bifida occulta), tenderness over spine (compressive myelopathy, e.g. in Pott's spine).

Diagnostic investigations in paraplegia depend on the suspected cause and site of lesion. *Spinal MRI* is essential

in all cases of spastic paraplegia, though spinal X-rays and CSF examination may be helpful in some cases. A positive *Queckenstedt test*, xanthochromic CSF and elevated proteins indicate spinal block (*Froin syndrome*), usually due to extramedullar tumors.

All cases with acute flaccid paraplegia should be reported for *AFP surveillance*, discussed below. and investigated accordingly. Chronic cases need EMG, muscle biopsy and serum CPK levels to exclude myopathies and NCV for neuropathies, as discussed in next chapter. Important d/d for common causes of acute flaccid paralysis in Indian children is given in **Table 10.36**.

Management of a paraplegic child aims to prevent secondary complications till primary cause is treated or the patient recovers spontaneously. Important steps in general care of a paralytic child includes: (a) maintenance of good nutrition, (b) care of the back/bowel and bladder, (c) physiotherapy and orthotic support, (d) prevention and treatment of intercurrent infections, e.g. pneumonia, (e) rehabilitation, and (f) psychological support.

Acute flaccid paralysis (AFP) surveillance is a critical component of national polio surveillance project since 1997, "*to detect all cases of wild polio virus disease and eliminate remaining foci of polio transmission*".

What is AFP? AFP is defined as "*any illness presenting with acute onset of flaccid paralysis in a child <15 years, for which no obvious cause such as trauma or electrolyte imbalance is found or a person of any age, with clinical suspicion of polio*". Generally, AFP of < 4 weeks is considered as acute.

Why all cases of AFP should be investigated? Since it is often difficult to exclude the diagnosis of poliomyelitis in a suspected case at the time of presentation, it is essential to investigate each case of AFP, to ensure that all cases are detected, reported and investigated and no case is missed out.

Components of AFP surveillance include: (a) reporting, (b) investigation of suspected case, and (c) outbreak-control measures after suspected case report.

All *Field reporting units, e.g.* district health centers or pediatric units of major hospitals must collect and send weekly reports of suspected case/s. *If no case is seen during reporting week, the report has to be sent as 'nil or zero report'*

Investigation of suspected AFP case includes: (a) *immediate reporting* to the designated person, (b) detailed data collection and *Line-listing of a*ll reported cases with a unique EPID number, to prevent duplication of reports, (c) *collection of stool cultures* for virus isolation, as specified earlier.

A stool sample should be collected (~8 gm or thumb size) from all cases presenting within 14 days of the onset of weakness (as early as possible) and transported to designated laboratory in ice pack (reverse cold-chain) under AFP surveillance program. A rectal swab may be collected from patients who do not pass stool within 24–48 hours of hospitalization.

Classification of an AFP case: All cases of reported AFP are classified after detailed epidemiological and viral studies as *Polio* or *non-polio* cases.

An AFP case is confirmed as *poliomyelitis only* if: (a) wild polio virus isolated from stool sample, or in absence of adequate stool sample, (b) cases continues to have residual weakness after 60 days of onset *or* 60 days-follow-up not available due to death or absence *and* expert review concludes that these cases could not be discarded as *non-polio* based on available data.

18.18 NEUROMUSCULAR DISORDERS

Neuromuscular disorders refer to a large heterogeneous group of diseases involving lower motor unit at various sites: (a) *anterior horn cells*, (b) *peripheral nerves,* (c) *myoneural junction,* and (d) *muscles.*

All neuromuscular disorders are characterized by generalized or localized flaccid weakness, hypotonia, and hyporeflexia, with/without sensory or autonomic involvement. The term *floppy child or infant* is usually reserved for a child with generalized hypotonia due to any cause, discussed later (Ch 18.19).

Clinical differentiation between neuropathies and myopathies is not always easy, though some important clues may be obtained on history, examination and basic investigations **(Table 18.39)**.

Some useful clinical indicators for different pattern of weakness in neuromuscular disorders in children are as follows:

- *Proximal muscle weakness* manifests with difficulty in getting up from chair, going up/down stairs, combing the hair.
- *Distal muscle weakness* manifests with difficulty in wearing slippers, buttoning/unbuttoning and holding the objects in hand.
- *Truncal weakness* presents with difficulty in turning on bed or sitting from supine position

TABLE 18.39: General D/D myopathies and neuropathies*

	Myopathies	*Neuropathies*
Family history	Common	Uncommon
Muscle weakness	Proximal	Distal (except SMA)
Muscle mass	Pseudohypertrophy	Atrophy
Deep reflexes	Depressed	Absent
Sensory involvement	Absent	Present
CPK levels	Abnormal	Near normal
EMG	Myopathic pattern	Neuropathic pattern
Muscle biopsy	Diagnostic	Non-specific

* based on usual features, though exceptions are common

- *Bulbar weakness* leads to difficulty in swallowing, nasal regurgitation, soft cry, dysphonia and recurrent aspirations.
- *Facial muscle weakness* manifests with difficulty in blowing balloons, sucking through straw and closing the eyes.

Important investigations in neuromuscular disorders include:

- ***Serum CPK levels*:** CPK is a lysosomal enzyme, released from damaged or degenerating muscle cells (N: <160 IU/L). These levels are markedly elevated (in thousands) in myopathies, though mild elevation is not uncommon in neuropathies.
- ***Nerve conduction velocity*** *(NCV)* is abnormal in neuropathies, only if >80% of nerve fibers are damaged. As NCV is slower in infancy than in older children, interpretation is difficult in this age group.
- ***Electromyography*** *(EMG),* as measured by insertion of a needle into the belly of partially involved muscle (atrophic or normal muscles should not be used for EMG) helps to differentiate neuropathies from primary myopathies, but does not identify the specific cause.

  Normally, the resting muscle is silent on EMG, while a triphasic record of motor unit action potential (MUAP) is obtained on its contraction. Important EMG abnormalities include:
  - Fasciculations or fibrillations in denervation lesions, e.g. spinal muscular atrophy;
  - Large amplitude, long duration MUAPs in peripheral neuropathies;
  - Low amplitude, short duration MUAPs in myopathies;
- ***Muscle biopsy*** is useful in suspected myopathies, which helps to differentiate primary myopathy from neuropathy as well as to identify the specific cause and enzyme deficiency.
- ***Nerve biopsy*** is indicated in probable neuropathic disorders. *Sural nerve,* just behind the lateral malleolus is preferred as it is a purely sensory nerve, supplies only a small area over lateral aspect of foot and regenerates rapidly in 90% cases even if injured.

18.18.1 ANTERIOR HORN CELL DISORDERS

Anterior horn cell (Motor neuron) disorders, may be congenital or acquired.

Spinal muscular atrophy is the commonest motor neuron disease in childhood, discussed belo, while other motor neuron disorders are very rare in children and include *amyotrophic lateral sclerosis*, *pontocerebellar hypoplasia*, etc. Motor neuropathies are also seen in many neurodegenerative disorders, e.g. gangliosidosis, ceroid lipofuscinosis, etc., though masked by more prominent signs of CNS or muscle involvement.

Poliomyelitis was once the commonest acquired anterior horn cell disease, discussed elsewhere (Ch10.21), though mild motor neuron involvement may also be caused by other enteroviral infections, e.g. Coxsackie and ECHO viruses.

Spinal muscular atrophy (SMA) is an autosomal recessive disorder of mutation in survival motor neuron (SMN1 and 2) genes located at chromosome 5q13.2. While SMN1 is responsible for synthesis of fully functional SMN protein for anterior horn cells, SMN2 largely produce non-functional proteins, with only 20% functional product.

In SMA, SMN1 is lost due to mutation and severity of the disease depends on number of SMN2 copies with more severe disease in cases with less SMN2 copies.

Pathologically, SMA denotes generalized, progressive degeneration of motor neurons (*anterior horn cells*) in spinal cord and brain stem nuclei. Upper motor neurons are normal.

Clinically, all variants are characterized by:

- Generalized symmetrical weakness with hypotonia, more prominent in proximal muscles but sparing extraocular muscles and sphincters.
- Muscle fasciculations, specially over tongue,
- Essential absence of tendon reflexes, and
- Normal intellect and alert child.

According to age of onset, four variants are known:

- ***SMA type I*** (*Werdnig-Hoffmann disease*) is the commonest type, which presents at *birth or within first 6 months of life* with feeding difficulties, poor cry and recurrent aspirations with respiratory infections. Most cases die in first 2 years of life.
- ***SMA type II*** (Late infantile disease) manifest by the end of first year with slowly progressive weakness leading to walking difficulties and scoliosis, along with fine finger tremors in some cases. Most of them survive beyond first decade of life before death due to aspiration.
- ***SMA type III*** (Juvenile form) is the mildest variant with adequate ambulation, except mild proximal muscle weakness specially at shoulders. Presence of fasciculations in affected muscles (specially tongue) and finger tremors are most important signs in these cases, which usually survive beyond mid-adulthood.
- ***SMA type IV*** with progressive bulbar palsy without significant spinal involvement is known but rare.

A functional classification of SMA also refers these cases as non-sitters (SMA1), sitters (SMA2 and severe SMA3) and walkers (early SMA3 and 4).

Diagnosis rests on demonstration of homozygous deletion in SMN1 gene, by multiplex ligation probe amplification (MPLA) in suspected cases.

Muscle biopsy is rarely required at present for diagnosis which reveals characteristic pattern of muscle denervation, i.e. presence of giant type I fibers with severely atrophic fibers. NCV may reveal axonal neuropathy, while muscle fibrillations may be present on EMG. CPK is normal or mildly elevated.

Prenatal diagnosis as well as postnatal confirmation of SMA is possible by molecular diagnostic studies in > 95% cases.

Treatment is largely supportive with control of respiratory infections, feeding support and physiotherapy, with orthotic support for ambulation and correction of scoliosis. Genetic counseling is essential to prevent the recurrence.

Recently three drugs have been approved for the treatment of SMA and prevent the progression of disease, including:

- *Onasemnogene abeparvovec* (zolgensma), a vector-based gene replacement drug to replace faulty *SMN1* gene, approved for use only in children < 2 years as a single dose intravenous infusion
- *Nusinersen* (Spinraza), an antisense oligonucleotide to enhance SMN2 copy numbers, given intrathecally (12 mg/dose) on day 0, 14, 28 and 63 at two-weekly intervals followed life-long every 4 months. Therapy should be started as early as possible before the deformities develop.
- *Risdiplam* (Evrysdi), a mRNA splicing modifier to enhance SMN2 copy numbers, given orally as 0.25 mg/kg/day to maximum of 5 mg/day above 20 kg body weight. Therapy should be started as early as possible before the deformities develop.

18.18.2 PERIPHERAL NEUROPATHIES

Neuropathies may be hereditary or acquired, generalized or localized and progressive or temporary **(Table 18.40)**. Pathologically, neuropathies may be *axonal* (damage to axons) or *demyelinating* (damage to myelin covering the axon), though the difference is largely electrophysiological. Axonal neuropathies are characterized by predominant distal weakness while demyelinating neuropathies present with distal as well as proximal weakness.

Some important peripheral neuropathies are discussed in this section, including Guillain-Barre syndrome–the commonest polyneuropathy in Indian children.

Guillain-Barré syndrome (GBS) is a post-infectious polyradiculoneuropathy characterized by acquired demyelination of motor and occasionally the sensory nerves, presenting as self-limiting, symmetrical, acute ascending flaccid paralysis.

According to pathological and electrophysiological characteristics, GBS is classified into 3 main subtypes — (a) acute inflammatory demyelinating polyneuropathy (AIDP), (b) acute motor axonal neuropathy (AMAN), and (c) acute motor and sensory axonal neuropathy (AMSAN). AIDP is commonest variant (80–90%) while AMSAN is the most severe disease.

TABLE 18.40: Important peripheral neuropathies

Congenital/Hereditary		
Motor	:	Spinomuscular atrophy
Mixed	:	HMSN, e.g. Charcot-Marie-Tooth disease Metachromatic leukodystrophies *Others:* Abetalipoproteinemia, porphyria
Autonomic	:	Familial dysautonomia (Riley-day syndrome)
Acquired		
Guillain-Barré syndrome		
Infections	:	Diphtheria, leprosy, bell palsy
Toxins	:	Lead and arsenic poisoning
Drugs	:	Isoniazid, vincristine, cisplatin
Others	:	Uremia, malignancies, Bell palsy, Vitamin B_{12} deficiency, vasculitic neuropathies

HMSN: Hereditary motor-sensory neuropathies

Incidence of GBS is 0.3–1.3/100000 children < 18 years of age.

Etiology: GBS is considered as an autoimmune reaction against protein component of the myelin, triggered by antecedent infections or vaccinations. Important infections associated with GBS include *Campylobacter jejuni;* viral infections, e.g. influenza, CMV, EBV and mycoplasma. GBS has also been reported following influenza, rabies, MMR and meningococcal vaccinations.

Clinically, history of preceding viral infection is present in ~60–70% cases, about 2–3 weeks before neurological manifestations, which include:

- Acute flaccid paralysis, typically *bilaterally symmetrical and ascending,* beginning from lower limbs with gradual involvement of trunk, upper limbs and bulbar muscles over few days. Deep tendon reflexes are usually absent but may be preserved in 30% cases.
- Respiratory failure due to bulbar, intercostals or diaphragmatic involvement in 20–30% cases.
- Paresthesia and pain in lower limbs is frequently present in early stages due to nerve root inflammation.
- Autonomic involvement with urinary retention and BP fluctuations in some cases.

Spontaneous recovery begins in 2–3 weeks from the last affected muscles and proceeds downwards. Recovery is usually complete and recurrent attacks are rare (<7%).

Rapid progression with maximum disability in 24 hours or persistent progression beyond 4 weeks suggests possibility of alternative etiology.

An uncommon variant of GBS, *Miller-Fisher syndrome* is characterized by a triad of Ataxia, areflexia and ophthalmological abnormalities.

Diagnosis depends on:

- Typical symmetrical neurological involvement,
- Abnormal CSF examination after the first week of illness, showing albumino-cytological dissociation in CSF, i.e. raised proteins and normal cell count.
- Abnormal nerve conduction studies after the first week of illness in 90% cases, suggestive of decreased NCV in AIDP variant and decreased muscle amplitude in AMAN variant.
- MRI spine with contrast imaging, showing selective anterior root enhancement, may be useful in early diagnosis of GBS, when electrophysiological findings are non-specific. It also helps to exclude other causes of AFP and myelopathy.
- Antiganglioside antibodies are present in 30% cases, though testing is not required in routine cases.

D/D of GBS includes other causes of acute flaccid paralysis **(Table 10.36)**.

Management of GBS includes:

a. Specific therapy with:

- *IV immunoglobulins* 400 mg/kg/day for 5 days (or 1 gm/kg/day for 2 days), given early in the course of disease, i.e. within 2 weeks of the onset of weakness.
- *Plasmapheresis* (200–250 mg/kg plasma on 5 alternate day sessions) to eliminate demyelinating antibodies and other mediators in severe cases, is useful only if done within 4 weeks of weakness. However, it is not more effective than IVIG therapy.

b. Supportive therapy with:

- Monitoring for progression of weakness.
- Management of respiratory insufficiency and autonomic complications
- General nursing care for nutrition, hygiene, etc.
- Physiotherapy during recovery phase.

Outcome: While majority of cases improve within 3–6 weeks, reported mortality rate is ~3–10% due to respiratory failure and autonomic dysfunction, while many other are left with residual weakness or chronic pains/disability.

Treatment-related fluctuation (TRF) may occur in 10%, i.e. progression of symptoms within 2 months of initial improvement/stabilization after therapy, who might benefit with repeat course of treatment. Recurrence is rare but may occur in ~2–5%. Influenza vaccination is contraindicated in children with past history of GBS.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) continues to progress beyond 4 weeks with relapsing-remitting course and concomitant sensory loss. Treatment includes long-term immunomodulator therapy with IVIG, steroids or repeated plasma exchange.

Other important neuropathies in children are as follows:

Hereditary neuropathies, though rare by themselves, account for ~70% of chronic peripheral neuropathies. Depending on prominent nerve involvement, this heterogeneous group may be divided into: (a) hereditary motor neuropathies, e.g. Spinal muscular atrophy (Ch 18.16.1), (b) hereditary motor and sensory neuropathies (HMSN), and (c) hereditary sensory and autonomic neuropathies, e.g. Riley-Day syndrome (Ch 18.18).

Peroneal muscular atrophy (Charcot-Marie-Tooth disease) is commonest hereditary motor and sensory neuropathy (HMSN-I), discussed here. Other HMSN are very rare and include *peroneal muscular atrophy of axonal type (HMSN-II), Dejerine-Sottas disease (HMSN-III), Roussy-Levy syndrome*, etc.

Charcot-Marie-Tooth disease is a predominantly autosomal dominant peripheral neuropathy, which typically present in late childhood or adolescence with gait abnormalities, but some cases may present as early as 2 years or as late as in mid-adulthood. Peroneal and tibial nerves are the earliest and most severely affected.

Clinically, it is characterized by-(a) progressive distal lower limb weakness, (b) wasting of peroneal muscles, i.e. *stork-neck deformity* of legs, (c) *foot drop* due to weakness of ankle dorsiflexors, and (d) *Pes cavus* with *hammer toe*. Sensory loss is limited to position (proprioception) and vibration sense. Ankle jerk is usually lost earlier than knee jerk. Involved peripheral nerves may be palpably enlarged.

Disease is very slowly progressive and most patients remain ambulatory till old age. In late stages, disease may also involve distal upper extremities with atrophy of forearm and hand (*claw-hand*). Proximal weakness is minimal and axial muscles are spared.

Diagnosis rests on-(a) characteristic distribution of weakness with peroneal atrophy, (b) typical combination of absent ankle jerk with normal knee jerk in early stages, (c) marked slowing of motor and sensory conduction on NCS, and (d) sural nerve biopsy showing reduced number of myelinated fibers with *onion-bulb formation* due to collagen and Schwann cell proliferation.

Treatment is supportive with physiotherapy in early stages to prevent contractures and orthotic correction for ankle stabilization with splinting/special shoes.

Metabolic neuropathies are rare in childhood, caused by-(a) inborn errors of metabolism, e.g. porphyria, abetalipoproteinemia, Refsum disease, etc. (b) nutritional deficiencies, e.g. thiamine deficiency, and (c) late metabolic disorders, e.g. diabetes and uremia; discussed in relevant chapters.

Toxic neuropathies, common in Indian children are:

Post-diphtheritic peripheral neuropathy is seen after 2–3 weeks of acute disease with loss of accommodation (occulomotor palsy) and bulbar involvement as earliest manifestations. Peripheral neuropathies are usually motor, symmetrical and often ascending, indistinguishable from GBS. Diaphragmatic paralysis is not uncommon.

Fig. 18.20: **Bell (Facial) Palsy.**

Drug-induced neuropathy is commonly seen with isoniazid (responds to pyridoxine), nitrofurantoin and anti-malignancy drugs, e.g. vincristine, cisplatin and cytosine arabinoside.

Heavy metal neuropathy is mostly associated with chronic lead poisoning, presenting as motor neuropathy, specially involving lower limbs.

Bell palsy is an acute unilateral infranuclear facial palsy as an isolated neurological defect, probably due to *postinfectious immune-mediated demyelination.*

Clinically, a classic case begins after 2–3 weeks of viral illness with acute onset of facial asymmetry and other signs of infranuclear facial palsy, sometimes associated with loss of taste in anterior 2/3rd of tongue. Exposure keratitis is common in unclosed eye. Most cases recover well in few weeks.

Diagnosis is clinical though other causes of infranuclear facial palsy, e.g. trauma, middle ear disease, facial nerve tumors and cerebrovascular insults must be excluded.

Treatment: Recovery is spontaneous, though corneal protection with lubricant eye drops, frequent facial massage (from below upwards) on affected side and supports to lift angle of mouth are advised during acute phase. Facial nerve stimulation may be used in cases with slower recovery. Other interventions, e.g. steroids and decompression of facial canal are of limited value **(Fig. 18.20)**.

18.18.3 NEUROMUSCULAR JUNCTION DISORDERS

Motor impulses from axonal terminals of peripheral nerves are transmitted to the muscles at motor end-plate, i.e. post synaptic muscle membrane, via release of *acetylcholine*. Acetylcholine activity in synaptic cleft depends on the amount of acetylcholine released from presynaptic terminals *or* the number of acetylcholine receptors on post-synaptic membrane. Acetylcholine is rapidly degraded by the cholinesterase enzyme and hence, cholinesterase inhibitors are commonly used in myasthenia gravis to increase acetylcholine concentration at myoneural junctions.

Myasthenia gravis is an uncommon but important chronic disorder of myoneural junction, characterized by *deficiency of acetylcholine receptors* and presenting with easy fatigability of muscles.

Etiology: Acetylcholine receptor deficiency in myasthenia gravis is almost always acquired (autoimmune), with presence of acetylcholine receptor antibodies. Many cases are associated with thymoma or other autoimmune disorders, e.g. SLE, rheumatoid arthritis, Hashimoto thyroiditis, etc.

Transient neonatal myasthenia may occur in infants of myasthenic mothers due to transplacental transfer of anti-acetylcholine receptor antibodies, which usually resolves spontaneously in next 3–4 months.

Clinically, *juvenile myasthenia gravis* usually present after 10^{th} year of life with:

- Ptosis and diplopia due to extraocular muscle weakness (earliest manifestation, most prominent in evenings or after exertion),
- Rapid fatigue of muscles after sustained/repetitive activity, e.g. opening and closing of grip.
- Dysphagia, dysarthria and chewing difficulties in more severe cases.

Muscular weakness progresses in severity with increasing age, leading to recurrent aspirations, respiratory infections and ultimately, respiratory failure and death in untreated cases.

Some cases may present with intermittent acute exacerbations of muscle weakness, i.e. *myasthenic crisis,* after viral infections or strenuous exercise, etc., which may life-threatening.

Neonatal myasthenia in infants of myasthenic mothers may present at birth with generalized floppiness, decreased spontaneous movements and feeding/respiratory difficulties, which improve gradually over few weeks.

Diagnosis is confirmed with:

- *Edrophonium (Tensilon) test:* Administration of a short-acting cholinesterase inhibitor, e.g. IV edrophonium chloride (0.1–0.2 mg/kg; max 10 mg) leads to rapid improvement in weakness, e.g. ptosis, within few seconds though effect lasts for only 1–2 minutes.

  Edrophonium test should not be done in young children due to the risk of arrhythmia and instead, neostigmine response test (IM 0.02–0.04 mg/kg) may be used, with maximum effect in 20–40 minutes.
- *Characteristic nerve conduction studies* showing decremental response on repetitive nerve stimulation, till the muscle becomes completely refractory; and

- *Anti-acetylcholine receptor (AChR) antibodies* in-50–60% of children and adolescent cases, (vs. in nearly all adult cases). Anti-muscle specific kinase (anti-MuSK) antibodies are present in ~40% of these sero-negative myasthenic children.

X-ray chest or CT of anterior mediastinum is indicated in all cases to exclude thymoma or thymic hyperplasia.

Treatment may be divided into symptomatic treatment and specific immunosuppressive therapy in autoimmune myasthenia.

- *Cholinesterase-inhibitors*, e.g. pyridostigmine (PO 1–5 mg/kg q4–6hr) is the treatment of choice for symptomatic relief and should be given 30 minutes before feeding to improve swallowing.
- *Immunosuppressive therapy* is indicated in cases with high acetylcholine antibody titers, preferably with long-term steroids. Prednisolone must be started with lower dose (PO 1.5 mg/kg/dose on alternate day), which needs to be escalated weekly till desired response. Other immunosuppressive agents, e.g. Azathioprine, cyclophosphamide, cyclosporine or mycophenolaate may be used as steroid-sparing agents or in refractory cases.
- *Other modalities*, e.g. IV immunoglobulins, pulse methylprednisolone, plasmapheresis and thymectomy are usually reserved for refractory patients or those with myasthenic crisis.
- Transient neonatal myasthenia due to maternal disease does not benefit from immunosuppressive therapy and should be treated only with pyridostigmine.
- *Avoidance of drugs* with myoneural toxicity, e.g. aminoglycosides, β-blockers, chloroquine, phenytoin and neuromuscular anesthetics, which may precipitate myasthenic crisis.

Prognosis is good in treated cases and spontaneous remission is common after few months or years.

Other uncommon neuromuscular junction disorders are as follows:

Congenital myasthenic syndromes are very rare and present at birth or at least before 2 years of life as floppy infant with hypotonia, limb weakness, ptosis, feeding and respiratory difficulties. *AChR antibodies* are absent in these cases with no benefits with steroid or other immunosuppressive therapy

Acute transient myoneural disorders are caused by pre-synaptic blockade of acetylcholine release, usually seen in organophosphorus poisoning, snake-bite, botulism and tick paralysis and discussed elsewhere.

18.18.4 MYOPATHIES

Myopathies are generally hereditary, though clinical manifestations may be delayed for variable period of time. Important myopathies are listed in **Table 18.41**. It is essential to understand difference between common 'muscular dystrophies' and rare 'congenital myopathies', as both may present at any age.

TABLE 18.41: Common myopathies in children

- **Hereditary/congenital**
  - *Muscular dystrophies*
    Duchhene muscular dystrophy (DMD/BMD)
  - *Others:* LGMD, FSHD, myotonic MD, congenital MD
  - *Developmental:* Congenital myopathies, benign hypotonia
  - *Metabolic:* Carnitine deficiency, GSDs
  - Mitochondrial myopathies, e.g. MELAS, MERRF
- **Acquired**
  - *Endocrinal:* Hypothyroidism, steroid-induced
  - *Metabolic:* Hypokalemic periodic paralysis
  - *Inflammatory:* Dermatomyositis

LGMD: Limb girdle muscular dystrophy, **FSHD:** Facioscapulohumeral dystrophy, **GSD:** Glycogen storage disorders, **MELAS:** Myoclonic epilepsy, lactic acidosis and recurrent stroke-like syndromes, **MERRF:** Mitochondrial encephalopathy with Red-Ragged fibers

Muscular dystrophies are essentially: (a) hereditary, (b) progressive, and (c) primary myopathies of *normally formed* muscles, excluding secondary involvement in neuropathies.

Congenital myopathies are: (a) hereditary or non-hereditary, (b) non-progressive, and (c) developmental defect or maturational arrest in formation of normal muscle.

Duchenne muscular dystrophy (DMD) is the commonest (1:3600 male live births) hereditary myopathy in Indian children, characterized by progressive weakness of mainly proximal lower limb muscles with pseudohypertrophy, leading to severe motor disability, loss of ambulation and usually death in second decade of life. A milder variant, i.e. *Becker muscular dystrophy* (BMD) presents at a later age with more gradual course. DMD and BMD together are also termed as Dystrophinopathies.

Etiology: DMD/BMD is an *X-linked recessive* disease with affected males and carrier females, due to deletion, duplication of point mutation of one or more exons of the *DMD* gene, located on Xp21 locus (*DMD* gene is the longest gene in human with 79 exons). However, 30% cases may be new mutations where mother is not a carrier. Girls are very rarely affected, if having Turner syndrome (single X chromosome) or random inactivation of normal chromosome (Lyon hypothesis).

Primary product of *DMD* gene is an important cytoskeletal protein – *Dystrophin*, present in skeletal and smooth muscles, brain and retina. This dystrophin is absent or severely deficient in DMD, while those with BMD have milder deficiency.

Clinical manifestations: Boys are asymptomatic at birth with normal early development including walking. In a typical case of DMD, weakness usually begins at ~ 2–3 years of age with:

Fig. 18.21A and B: **Duchenne muscular dystrophy: Psuedohypertrophy of calf muscles.**

- *Mild waddling (Trendelenburg) gait* with a lordotic posture to adopt for gluteal weakness.
- *Positive Gower sign*, i.e. difficulty in standing from recumbent position due to pelvic girdle weakness. When asked to do so, he typically turns to his side, lifts his trunk up by supporting his weight on his arms and then stands up as if climbing upon his body with hand support.
- *Pseudohypertrophy* of calf muscles with wasting of thigh muscles **(Fig. 18.21)**. Tongue and forearms may also develop pseudohypertrophy. Distal deep jerks, e.g. ankle and brachioradialis are stronger than proximal knee or biceps/ticeps jerks.
- *Progressive weakness of proximal muscles* including respiratory involvement with weak cough and recurrent respiratory infections, and/or pharyngeal muscle weakness with recurrent aspirations, nasal twang and regurgitation. Distal muscle functions, e.g. writing, etc. are spared till terminal stage.
- ***Associated features***, e.g. *cardiomyopathy and mild mental retardation* or learning disabilities are present in nearly all cases with variable severity, not necessarily correlating with severity of muscular disease. Cardiomyopathy usually appears at ~10 years, though CCF and arrhythmia are uncommon till terminal stage and usually precipitated by intercurrent infections. Intermittent gastric dilatation with abdominal pain and vomiting is common.

Course: Patient gradually becomes bedridden by 7–10 years of age with development of contractures and scoliosis and die by 15–20 years due to respiratory failure, aspiration or CCF.

Carriers are asymptomatic but may have myalgia, cramps and mild calf hypertrophy in 10% cases.

Becker muscular dystrophy, the milder variant, usually present in late childhood with inability to raise the hand above shoulder (e.g. during combing the hair), remain ambulatory till 15–20 years and survive till 4th–5th decade.

Diagnosis may be made clinically on the basis of: (a) positive Gower sign, (b) proximal muscle weakness with pseudohypertrophy, and (c) similar family history, supported by markedly elevated *CPK levels.* CPK levels are high (>10 times of normal) even in asymptomatic cases and assist in early diagnosis of the disease in siblings. Carriers have mild CPK elevation.

Confirmation requires genetic diagnosis with multiplex PCR or MPLA to detect deletion or duplication in the *DMD* gene, though next generation exome sequencing (NGS) may be needed to detect point mutations in some cases.

Muscle biopsy is no longer necessary in genetically proven cases, but may reveal: (a) scattered degenerating and regenerating myofibrils, (b) endomysial connective tissue proliferation, and (c) focal mononuclear infiltration. It also helps to differentiate DMD (no dystrophin staining) from Becker dystrophy (reduced and patchy staining) on immunohistochemistry.

Dystrophin levels are <3% of normal in classic DMD and 20–90% in Becker dystrophy.

EMG is indicated only in doubtful cases with near normal CPK levels, which reveals low amplitude and duration of motor action potential.

Carrier detection is possible by: (a) pedigree charting, (b) mild elevation of CPK levels in 80% cases, (c) muscle biopsy in suspected carriers, and (d) detection of dystrophin mutations in blood samples.

Prenatal diagnosis is possible as early as by 12 weeks PCR/MPLA testing on chorionic villi samples.

Management is entirely supportive at present, though experimental studies after discovery of dystrophin molecule are promising.

- *Supportive treatment* includes:
  - Nutritional support (but avoid obesity),
  - Physiotherapy to prevent/delay contractures,
  - Ambulatory support (wheel chair/orthotic braces),
  - Calcium supplements to prevent osteoporosis,
  - Treatment of respiratory infections and CCF,
  - Psychological support.
- *Steroids* (PO prednisolone 0.75 mg/kg/d for 10 days a month) have shown temporary improvement in muscle weakness for 4–6 months by decelerating the rate of myofiber necrosis. However, it does not alter the ultimate course and exact role is controversial.
- *Newer and promising interventions* in selected cases include:
  - *Antisense oligonucleotide drugs*, e.g. *Drisapersen* and *eteplirsen*, which induce exon-skipping during splicing of mRNA to produce a shorter but potentially functional dystrophin protein and have been approved for use in selected cases.
  - Ataluren, another drug approved for non-sense mutation, binds to ribosomes and enables stop codon read through.
  - *Other experimental therapies* include: (a) myoblast transfer therapy from a near relative, or (b) recombinant dystrophin gene therapy.
- *Prenatal screening and counseling* is the best strategy so far to counter this disease.

Some other important myopathies in children are as follows:

Limb girdle muscular dystrophy (LGMD) is a group of slowly progressive inherited disorders, mainly affecting muscles of hip and shoulder girdle. Some of them are autosomal dominant (LGMD-1) while others are recessive (LGMD-2). A mutant dystrophin-related protein (*sarcoglycan*) has been associated with autosomal recessive disease with characteristic *sarcoglycanopathy* on muscle biopsy.

Most cases present in adolescence with gluteal muscle weakness leading to back pain and lordosis and progress gradually to non-ambulatory state by 3rd decade. Calf hypertrophy is common. Simultaneous weakness of shoulder and neck muscles is common, though facial, ocular and bulbar paralysis is rare. Intelligence is normal.

Facioscapulohumeral dystrophy (autosomal dominant involving chromosome 4q35) is a relatively benign disorder, which manifests at around puberty with facial weakness (inability to close eyes, smile, whistle), shoulder girdle weakness (scapular winging) and upper limb weakness (inability to comb the hair). Weakness is slowly progressive with gradual involvement of pelvic girdle (*Gower sign*).

Unlike DMD, pseudohypertrophy is absent, cardiomyopathy is rare and intelligence is spared. CPK is mildly elevated and EMG/muscle biopsy suggests coexisting neurogenic pathology. Diagnosis rests on genetic testing and treatment is supportive.

Myotonic muscular dystrophy (autosomal dominant involving DMKP gene on chromosome 19) is the second commonest muscular dystrophy after DMD in Europe, USA and Australia, though rare in India.

Clinically, these cases manifest with—(a) typical facial features (tented upper lip), (b) progressive weakness of distal muscles, e.g. hands, starting after infancy. Presence of *myotonia*, i.e. slow relaxation of muscles after contraction (e.g. slow release of grip) is pathognomonic though develops only after 10 years of age. Multi-systemic involvement with mental retardation, cardiomyopathy, cataracts, endocrinal disorders and immunodeficiency is common.

A rare variant presents in neonatal period with severe hypotonia (floppy infant), facial wasting and feeding/breathing problems. Most cases die in infancy.

CPK and EMG are usually normal in children, while EMG may demonstrate myotonia in older patients. Diagnosis rests on genetic testing and treatment is supportive.

Congenital muscular dystrophies (autosomal recessive) encompass many distinct disorders, all with severe diffuse hypotonia (floppy infant) and proximal muscle weakness at birth. Facial, ocular and bulbar muscles are relatively spared. However, further course is slowly progressive and many cases are able to stand and walk with support in late childhood, unless contractures have developed. CNS involvement is common with mental retardation and white matter changes on MRI. CPK is moderated elevated and muscle biopsy shows signs of muscular dystrophy with *merosin* deficiency on immunohistochemistry.

Fukuyama disease, the commonest congenital muscular dystrophy, is the second commonest cause of muscular dystrophy in Japan (after DMD), associated with severe cardiomyopathy, microcephaly, mental retardation, seizures and ocular abnormalities.

Developmental muscle disorders may be isolated or associated with other congenital anomalies. Some important developmental disorders include:

Congenital absence of muscles is usually unilateral, e.g. absence of pectoralis major (*Poland syndrome* with associated amastia, rib deformities, webbed fingers and radial nerve aplasia), sternocleidomastoid (torticollis), depressor angularis oris (facial asymmetry on crying), etc. Asymptomatic absence of *palmaris longus* muscle of ventral forearm is present in ~ 30% population.

Proteus syndrome (*Elephant man*) is an extremely rare disorder of ecto/mesodermal overgrowth, with

asymmetric overgrowth of extremities including muscle hypertrophy, bony thickening, angiomas, cutaneous lesions, and hemi-megalencephaly.

Benign congenital hypotonia is clinical term to denote generalized *non-progressive hypotonia without weakness, hyporeflexia* or developmental delay. Intelligence is normal. Diagnosis rests on exclusion of congenital myopathies on muscle biopsy. Prognosis is good, except persistence of hypotonia which may lead to recurrent joint dislocations or injuries. Many of them are circus artists or gymnasts.

Congenital myopathies is a heterogeneous group of rare disorders, all characterized by *defective development or arrested maturation* of muscles (d/d muscle dystrophies, in which initial muscle development is normal). Important examples are *myotubular myopathy* (X-linked), *congenital muscle fiber-type disproportion* (usually sporadic), *nemaline-rod myopathy* (AR), *central core disease* (AD).

Clinically, congenital myopathies are non-progressive and usually present—(a) at birth or in early infancy as floppy child, or (b) in late childhood, with delayed motor development or defective ambulation (proximal girdle weakness). Facial and ocular muscles are frequently affected with feeding and breathing difficulties in severe cases. *Unlike DMD, affected muscles are wasted rather than pseudohypertrophic*. Central core disease is consistently associated with malignant hyperthermia.

Diagnosis is based on muscle biopsy including electron microscopy, as CPK levels are frequently normal and EMG changes are non-specific.

Treatment is non-specific and supportive. Severely affected children die in early infancy due to aspiration or respiratory insufficiency. Mild cases are non-progressive but may require orthotic/ambulation support.

Inflammatory myopathies, characterized by skeletal muscle inflammation > muscle fiber damage >weakness; may be postinfectious (influenza or HIV virus, toxoplasmosis, bacterial) or autoimmune in origin (dermatomyositis, polymyositis, eosinophilic myositis). Dermatomyositis is the leading cause of inflammatory myopathy in children.

Endocrinal myopathies in children are not as common as in adults, seen in hypothyroidism, thyrotoxicosis, primary hyperparathyroidism and steroid-excess, e.g. prolonged steroid therapy or Cushing disease. Most of them are associated with muscle wasting, except *Kocher Debre semelaigne syndrome,* i.e. generalized pseudohypertrophy in some cases of hypothyroidism.

Metabolic myopathies may be seen in many inborn errors of metabolism, e.g. glycogenoses (type I-V and VII) or lipid disorders (Carnitine deficiency), discussed elsewhere. Two other important causes include:

Hypokalemic periodic paralysis, an autosomal dominant disease, characterized by recurrent episodes of sudden and generalized weakness of skeletal muscles, with transient hypokalemia. Each episode lasts for few minutes to few hours and patient is normal between attacks.

Serum potassium, EMG and muscle biopsy (vacuolar myopathy) is abnormal only during attacks. Attacks may become more frequent in adulthood, leading to permanent and progressive myopathy. Hypokalemia due to other causes, e.g. renal tubular acidosis or hyperaldosteronism (*Conn syndrome*) may also cause transient and intermittent paralysis.

Rarely, similar episodes are known with transient hyperkalemia (*hyperkalemic periodic paralysis*), specially in cases of chronic renal failure, or excessive potassium supplementation.

Mitochondrial myopathies are part of systemic mitochondrial disorders due to point mutations in mitochondrial or nuclear DNA, leading to altered aerobic metabolism in various cells with secondary histopathological abnormalities. Brain and muscles are most affected. Mitochondrial DNA mutations disorders *are exclusively inherited from mothers.* Important mitochondrial myopathies include:

- ***MELAS*** (***M***itochondrial myopathy, ***E***ncephalopathy, ***L***actic ***A***cidosis and ***S***troke-like episodes) usually presents as a degenerative disorder with—(a) delayed motor and cognitive development, (b) recurrent hemiplegia/hemianopia (stroke-like episodes) and/or seizures, (c) episodic vomiting, seizures and progressive dementia. Muscle biopsy reveals typical *ragged-red fibers*. Most cases manifest in late childhood and die in few years.
- ***MERRF*** (***M***itochondrial ***E***ncephalopathy with ***R***ed-***R***agged ***F***ibers) present with myoclonic seizures, progressive myopathy (with *red-ragged fibers* on biopsy) and cerebellar signs in late childhood or adults with/without dementia and other features.

18.19 FLOPPY INFANT

The term *Floppy infant* or child denotes a '*baby with generalized hypotonia*', irrespective of the etiology.

Clinically: These cases characteristically present with bizarre or unusual postures, increased range of passive joint movements, paucity of spontaneous movements and delayed motor milestones. Newborns who are hypotonic *in utero* may be born with hip dislocation, arthrogryposis or both. In addition, many of these infants have poor sucking, swallowing and breathing difficulties suggestive of facial or bulbar muscle involvement.

Mothers of the newborns with hypotonia may perceive reduced or delayed fetal movements and may have associated polyhydramnios.

Important signs of floppiness include:

- *Postural abnormalities*, e.g. (i) *frog-like posture* in vertical suspension, (ii) *head lag* in pull-to-sit maneuver, and

TABLE 18.42: Causes of floppy infant/child

- **Cerebral disorders**
  - Perinatal hypoxic-ischemic brain injury
  - *Chromosomal:* Down syndrome
  - Atonic cerebral palsy
  - *IEMs:* Mucopolysaccharidosis, cerebral lipidosis
- **Spinal disorders**
  - Spinal muscular atrophy (Werdnig-Hoffmann disease)
  - Poliomyelitis
- **Peripheral neuropathies**
  - Guillain-Barré syndrome
  - HMSN, e.g. Charcot-Marie-Tooth disease
  - Familial dysautonomia (Riley-Day syndrome)
  - *Toxic:* diphtheria, lead poisoning, drugs
  - *Metabolic:* Thiamine deficiency, IEMs
- **Disorders of myoneural junction**
  - Myasthenia gravis
  - *Toxins:* Botulism, organophosphorus poisoning
- **Disorders of muscles**
  - Muscular dystrophies, e.g. DMD, others
  - Congenital myopathies or benign congenital hypotonia
  - *Metabolic:* GSDs, carnitine deficiency
  - *Endocrinal:* Hypothyroidism
- **Miscellaneous**
  - Prematurity
  - *Nutritional:* Rickets, PEM
  - *Collagen disorders:* Ehlers-Danlos syndrome

IEM: Inborn errors of metabolism, **HMSN:** Hereditary motor sensory neuropathies, **DMD:** Duchenne muscular dystrophy, **GSD:** Glycogen storage disorders

(iii) *Rag-doll* appearance on ventral suspension, due to head lag, marked curving of back and limp limbs.

- *Lack of passive tone*, e.g. (i) flabby muscles on palpation, and (ii) excessive range of passive movements, e.g. wide popliteal angle or heel-to-ear maneuver.
- *Lack of active tone*, e.g. poor arm/leg recoil. *d. Paucity of spontaneous movements*.

Etiology: Generalized hypotonia usually indicate peripheral neuromuscular disorders, though some cases have cerebral hypotonia or idiopathic origin **(Table 18.42)**.

Diagnostic approach in a floppy child involves:

- ***Clinical localization,*** specially differentiation between neuropathies and myopathies (*see* **Table 18.37)**.
  - *Cerebral hypotonia* is typically static and associated with *brisk reflexes*. Facial dysmorphism, mental retardation and congenital anomalies are common, suggestive of possible chromosomal defects.
  - *Spinal or anterior horn cell disorders, e.g. spinal muscular atrophy* (SMA) are commonest cause of floppy infant, characterized by: (a) symmetric weakness with hypotonia, sparing extra-ocular muscles and sphincters, (b) muscle fasciculations, specially over tongue, (c) absent tendon jerks, and (d) normal intellect and alert child (Ch 18.18.1).
  - *Peripheral neuropathies, e.g. GBS* are usually acquired and present after infancy with: (a) predominantly distal weakness, (b) marked atrophy, and (c) absent deep reflexes. Sensory involvement is common. (Ch 18.18.2)
  - *Myopathies, e.g. DMD* are generally characterized by—(a) predominantly proximal weakness, (b) pseudohypertrophy with advancing age, and (c) depressed but present deep reflexes. *Myotonia*, i.e. slow release of grip, may be present in some myopathies. (Ch 18.18.4)
  - *Neuromuscular junction disorders,* e.g. myasthenia presents with—(a) predominant facial weakness with ptosis, ophthalmoplegia and bulbar weakness, (b) diurnal variation in weakness, and (c) increasing weakness on repetitive activity, e.g. gripping/ungripping of objects. (Ch 18.18.3)
- ***Specific investigation*** depends on the probable cause. While CPK estimation, NCS and EMG is indicated in most cases, *karyotyping* for chromosomal disorders, e.g. Down syndrome, *thyroid function tests* for hypothyroidism, *edrophonium test* for myasthenia gravis, and *biochemical enzyme studies* for inborn errors of metabolism are necessary in selected cases.

Cardiac evaluation with ECG is important in suspected myopathies for early diagnosis of associated cardiomyopathies and conduction defects.

18.20 DISORDERS OF AUTONOMIC SYSTEM

Autonomic nervous system (ANS) is mainly concerned with innervation of unstriated muscles in internal viscera and secretory glands. Although isolated ANS disorders are extremely rare in childhood, ANS disturbances are commonly seen in many neurological and metabolic disorders, poisonings and during drug therapy.

ANS includes two anatomically different and physiologically antagonistic components: (a) *sympathetic* system, and (b) *parasympathetic* system. Anatomically, both components include: (a) pre-ganglionic neurons, (b) ganglions, and (c) post-ganglionic neurons, though other characters are markedly different in two systems **(Table 18.43)**.

While ANS involvement is common in many disorders, familial dysautonomia or *Riley-Day syndrome* is the commonest primary autonomic neuropathy, discussed here.

Riley-Day syndrome (familial dysautonomia) is an autosomal recessive disorder, especially in jews, characterized by sensory and autonomic neuropathy.

Clinical manifestations begin in infancy with feeding difficulties and recurrent aspirations, though more definitive features develop by 2–3 years, including:

- *Autonomic crises*, i.e. recurrent episodes of *cyclic* vomiting, hypertension, profuse sweating, skin blotching, temperature fluctuations and irritability, each lasting for few days.

TABLE 18.43: Important differences between sympathetic and parasympathetic ANS

	Sympathetic	*Parasympathetic*
Anatomical Features		
Pre-ganglionic outflow#	Thoraco-lumbar	Cranio-sacral
Location of ganglions	Paravertebral	Near innervated viscera
Post-ganglionic innervation	Visceral	Visceral
Neurotransmitter	Adrenergic*	Cholinergic
Physiological effects		
Pupil	Dilatation	Constriction
Heart rate	Tachycardia	Bradycardia
Peripheral vessels	Vasoconstriction	Vasodilatation
Blood pressure	Increases	Decreases
Bronchi	Relaxation	Constriction
Bowels	Constipation	Diarrhea
Bladder	Retention	Evacuation
Metabolic	Hyperglycemia	Hypoglycemia
Skin/mucus membranes	Pili erection, sweating	Lacrimation, salivation

*except for sweat glands

#Preganglionic outflow from spinal cord is mainly thoracolumbar (from T_1–L_1) for sympathatic system and craniocaudal (along the cranial nerves III, VII, IX, X and from sacral S_{2-3}) for parasympathatic system.

- *Sensory* ataxia and insensitivity to pain, with trophic and corneal ulcers.
- *Seizures* in ~ 40% cases.

Diagnosis is clinical, though *positive methacholine challenge test*, i.e. miosis after 10–20 minutes of conjunctival instillation of 2.5% methacholine, may be used to support the diagnosis.

Treatment is symptomatic and supportive with topical eye lubricants, anti-emetics, (e.g. chlorpromazine), prevention of injuries to anesthetized parts and vital system support. IV immunoglobulins have shown promising results in severe cases.

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CHAPTER

19

Hematological Disorders

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19.1 BASIC CONSIDERATIONS

Normal blood volume in children is ~80 ml/kg, of which ~45% is contributed by various cellular elements, i.e. *red blood cells (RBCs), while blood cells (WBCs) and platelets*, rest being the *plasma*. Important functions of blood include transport of gases and metabolites (RBCs and plasma), immunological defenses (WBCs) and hemostasis (platelets).

Developmental hematopoiesis: While fetal hematopoiesis begins as early as in the 3rd week, normal hematological values *in utero* and in postnatal life vary according to the physiological needs of baby. Some important aspects of hematopoiesis in general and in different age groups, are as follows:

Site: Fetal hematopoiesis is mainly *extramedullary* till late gestation, i.e. in extra-embryonic yolk sac from 10–14th day to 6–8 weeks and in liver and spleen from 6–8 weeks to 20–24 weeks. Bone marrow gradually takes over this function from 20–24th weeks onwards. Virtually all marrow cavities in body are involved in hematopoiesis at birth, but gradually this function moves to central bones, e.g. sternum, pelvis, vertebrae and ribs. Remaining marrow in the extremities and skull is replaced by fat. However, hematopoietic cells continue to exist in liver, spleen and other medullary sites and get reactivated during the state of increased needs (extramedullary erythropoiesis in hemolytic anemia).

Regulators: Bone marrow is populated by hemangioblasts, i.e. pluripotent stem cells (PSC) and descendent cell-lines, i.e. myeloid, erythroid, and megakaryocytic lineage at various levels of maturity **(Fig. 19.1)**. Predominance of a cell-line produced at any stage, depends on the needs of fetus/baby and guided by various cytokines (growth factors), e.g. *erythropoietin* (for RBCs), *colony stimulating factors* (G-CSF, GM-CSF and M-CSF) and *interleukins* $IL_{1–16}$ (for leukocytes) and *thrombopoietin* (for platelets).

Erythropoiesis: Important steps in marrow erythropoiesis include differentiation of PSC into *erythroid colony forming units* (CFU-E) and formation of erythroblasts (earliest

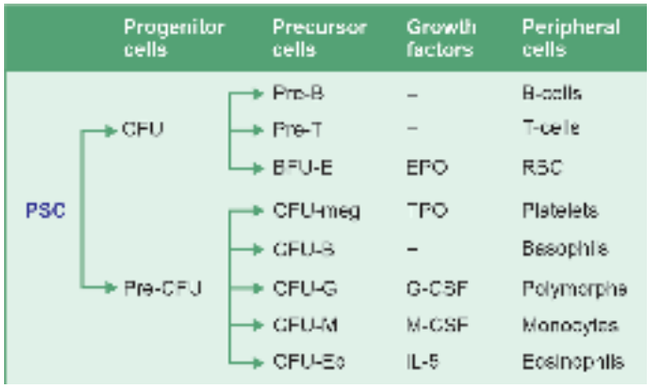

Fig. 19.1: Hematopoietic cell differentiation.
PSC: Pluripotent stem cell; **BFU:** Burst forming unit; **CFU:** Colony forming unit; **EPO:** Erythropoietin; **TPO:** Thrombopoietin; **CSF:** Colony stimulating factors; **IL:** Interleukin

in vivo cell of erythroid series), which mature through various stages into *normoblast* – the last nucleated cell of erythroid series. Normoblasts further mature with extrusion of nucleus to form *reticulocytes* (earliest non-nucleated cell of erythroid series), which retains its capacity for hemoglobin synthesis till released into circulation and matures as RBC.

Hematopoiesis is an enormously regulated process, with >10 billion erythroid and myeloid cells produced per hour, sustained throughout life by slowly cycling quiescent pool of hematopoietic stem cells. These stem cells have the capacity to self-renew and to commit to one of the 10 hematopoietic lineages by a stochastic process that induces a proliferation and differentiation program driven by expression of sets of transcription factors.

Mature RBCs, although devoid of nucleus, mitochondria and hemoglobin synthesis capacity, continue to function for a normal life span of ~120 days, before elimination of senescent cells by liver and spleen. However, fetal and neonatal RBCs have a shorter life span of ~30–60 days and ~60–90 days respectively.

Rate of erythropoiesis is primarily controlled by *erythropoietin* (EPO)-a hormone produced by

juxtaglomerular apparatus of kidney in response to hypoxia, which stimulates differentiation of PSC into erythroid precursors. During fetal life, EPO is produced in liver.

Fetal hematopoiesis is primarily erythroid in nature, due to higher oxygen requirements and lower oxygen tensions in transplacental blood (60–65%). At birth, newborns have higher hemoglobin and hematocrit levels, which progressively decline in early postnatal period due to: (a) shorter life span of fetal RBCs, and (b) transient EPO suppression due to better oxygenation. This drop nadirs at ~2–3 months (*physiological anemia*) before resumption of the normal rate of erythropoiesis and restoration of hemoglobin levels.

Hemoglobin (Hb) is a tetramer molecule with two pairs of polypeptide globin chains, each having a heme group attached to it. Human Hb contains different combinations of these polypeptide chains during various stages of development that differ from each other in their amino acid structure and designated as – α, β, γ, δ, ξ (zeta), ε (epsilon) chains **(Table 19.1)**. While α gene is located on chromosome 16, β, γ, and δ genes are closely linked to chromosome 11.

At birth, 70% of Hb is fetal Hb (HbF), which differs from adult Hb in terms of—(i) higher affinity to oxygen, and (ii) resistance to acid as well as alkali (used as a diagnostic test).

A *switch-over* from fetal to adult Hb synthesis in late intrauterine and early postnatal life leads to gradual decline in HbF levels during infancy and its replacement by adult Hb.

Adult Hb includes two different hemoglobin forms-predominant HbA and HbA_2. HbA is detectable by 12–16 weeks and prenatal diagnosis of thalassemia is possible at this age. At birth, 30% of Hb is HbA and rapidly increases to contribute >95% of total Hb by late infancy. HbA_2 is <1% at birth and ~2.0–3.4% of total Hb after infancy.

Leukopoiesis involves differentiation of PSC into lymphocytes and granulocytes (polymorphs, eosionophils, basophils, monocytes), regulated by various cytokines, i.e. *GM-CSF, G-CSF, M-CSF and interleukins* **(Fig. 19.1)**. Except T-lymphocytes, which leave bone marrow in early stages to mature in thymus, other leukocytes mature in marrow itself before entering the circulation and populating various tissues. Nucleus of younger polymorphs is less segmented (*Band forms*) than that of mature cells.

As fetus lives in relatively sterile environment, need for intrauterine leukopoiesis is limited and neutrophils are virtually absent till last trimester, when there is sudden surge in granulocyte formation. Consequently, preterms are more susceptible to infections than term newborns. While there is some drop in peripheral leukocyte and polymorph counts during first 1–3 months, postnatal bone marrow contains 2–5 times more cells of myeloid series than those of erythroid series. This includes a large pool of mature neutrophils, which may be released rapidly in circulation during acute infections.

Thrombopoiesis: Platelets develop from breakage of megakaryocytes-the large cells with abundant DNA, which differentiate from PSC and mature under the influence of *Thrombopoietin*. Normal platelet count remains unchanged from 18th week of gestation onwards, between 1.5–4.5 lac platelets/mm^3.

TABLE 19.1: Human hemoglobins at different ages

Embryonic Hbs *(during first 3 months of gestation)*	
Gower 1	(ζ_2 ε_2)
Gower 2	(α_2 ε_2)
Portland	(ζ_2 γ_2)
Fetal Hb *(predominant from 8th week till birth)*	
Hb F	(α_2 γ_2)
Adult Hb *(predominant postnatal Hb)*	
Hb A	(α_2 β_2)
Hb A_2	(α_2 δ_2)

Normal Hematological Characteristics

Complete blood counts and peripheral smear examination are two most valuable investigations in hematology and correct interpretation of these reports is essential with due considerations to developmental and other physiological variations.

Complete blood count (CBC) usually include six basic parameters: (i) hemoglobin, (ii) hematocrit (or packed cell volume), (iii) RBC count, (iv) total and differential WBC counts, (v) platelet counts, and (vi) erythrocyte sedimentation rate. Normal values of some of them with age-wise variations are given in **Table 19.2**.

TABLE 19.2: Normal hematological values

	Hb *(gm/dl)*	*Hct* *(%)*	*TLC* *(cells/mm^3)*	*PMN* *(%)*
At birth	16.8 (13.7–20.1)	55 (45–65)	18,000 (9,000–30,000)	61% (40–80%)
<2 wks	16.5 (13.0–20.0)	50 (42–66)	12,000 (5,000–21,000)	40% (40–80%)
3–6 mo	12.0 (9.5–14.5)	36 (31–41)	12,000 (6,000–18,000)	30% (40–80%)
1–6 yrs	12.0 (10.5–14.0)	37 (33–42)	10,000 (6,000–15,000)	45% (40–80%)
6–12 yrs	13.0 (11.0–16.0)	38 (34–40)	8,000 (4,500–3,500)	55% (40–80%)
>12 yrs	14.0 (12.0–16.0)	42 (37–47)	7,500 (5,000–10,000)	55% (35–70%)

Hct: Hematocrit; **TLC:** Total leukocyte count; **PMN:** Polymorphonuclear cells.

Peripheral smear (PS) is an extremely valuable screening test in hematology and infections. A freshly prepared and stained (hematoxylin-eosin staining) should be examined for:

- RBC morphology, e.g. shape, size, color and inclusion bodies, e.g. parasites,
- Differential WBC counts and their morphology, and
- Presence of platelet clumps. Absence of platelet clumps on PS is an indicator of thrombocytopenia, though should be confirmed by platelet count.

Important PS changes in various hematological disorders have been discussed in respective chapters.

19.2 ANEMIA-GENERAL CONCEPTS

Anemia is defined as a *reduction in haemoglobin concentration* below the age-related norms **(Table 19.3)**.

NFHS-5 shows that about two-third of Indian children aged 6–59 months (67.11%) are anemic with Hb <11 gm/dl. Prevalence of anemia in pregnant mothers at similar Hb cut-off is 52.2%.

Etiology: Anemia is a clinical manifestation of imbalance between production and loss of RBCs, due to any cause **(Table 19.4)**.

Production may be impaired due to bone marrow failure (*Aplastic/hypoplastic anemia*) or deficiency of various substrates required for production of Hb (*Nutritional anemia*).

Similarly, increased loss of RBCs may be due to acute or chronic bleeding (*hemorrhagic anemia*) or accelerated destruction in reticuloendothelial system (*hemolytic anemia*).

Pathophysiology: Irrespective of etiology, the prime event in anemia is *impaired oxygen carrying capacity* of blood with consequent tissue hypoxia. However, clinical manifestations do not appear until Hb levels drop <7–8 gm%, due to various compensatory physiological adjustments as follows:

- *Hemodynamic adjustments* with tachycardia, increased cardiac output and hyperdynamic circulation to maintain adequate O_2 supply despite lower carrying capacity.
- *Shift of O_2 dissociation curve towards right*, i.e. reduced Hb affinity for O_2 due to increase in 2,3-DPG concentrations in RBCs, which permits release of more oxygen at cellular level.
- *Stimulation of EPO activity* with increased erythropoiesis, which may or may not be effective, depending on marrow response and availability of substrates. It also stimulates extramedullary erythropoiesis in chronic anemia, e.g. hemolytic anemia.

Clinical presentation depends on the severity of anemia and rapidity of its development. Primary indicators of anemia, irrespective of its etiology include:

- *Pallor* is first visible over conjunctiva and oral mucus membranes and distribution of pallor is used to classify severity of anemia as per WHO classification.

  Severity of pallor over palms is used to classify anemia under IMNCI guidelines as—(a) *severe anemia*, with severe palmar pallor, (b) *some anemia*, with some palmar pallor, and (c) no anemia, without palmar pallor.
- *Signs of cellular hypoxia*, e.g., easy fatigability, growth failure, lack of attention span, dizziness, etc.
- *Signs of cardiac decompensation*, e.g., tachycardia, collapsing pulse, functional murmurs, cardiomegaly, congestive cardiac failure, etc. ECG changes of myocardial hypoxia may be present in severe anemia, including depressed ST segment with flat/inverted T waves.
- *Signs of compensatory erythropoiesis*, e.g., hepatosplenomegaly, hemolytic facies and skeletal changes are most prominent in hemolytic anemia.

TABLE 19.3: WHO cut-off points (Hb%) for anemia–2011

Age	*Normal*	*Anemia*		
		Mild	*Moderate*	*Severe*
6–59 mo	≥11	10–10.9	7–9.9	<7
5–11 yrs	≥11.5	11–11.4	8–10.9	<8
12–14 yrs	≥12	11–11.9	8–10.9	<8
Pregnancy	≥11	10–10.9	7–9.9	<7
Adult female	≥12	11–11.9	8–10.9	<8
Adult male	≥13	11–12.9	8–10.9	<8

TABLE 19.4: Etiological classification of anemia

- **Inadequate bone-marrow production**
  - Aplastic anemia
  - Pure red cell aplasia
  - Transient erythroblastopenia
  - Chronic infections/inflammation/renal disease
  - Marrow infiltration: Malignancies, storage disorders
- **Substrate deficiencies (Nutritional anemia)**
  - Iron deficiency anemia
  - Megaloblastic anemia (Folic acid, Vitamin B12)
  - Other nutrient deficiencies (PEM, Vitamin C, Zn)
  - Malabsorption syndrome
- **Increased destruction (Hemolytic anemia)**
  - Intra-corpuscular (congenital)
    - *Membrane defects:* Hereditary spherocytosis
    - *Enzyme defects:* G6PD deficiency
    - *Hemoglobinopathies:* Thalassemia, sickle cell anemia
  - Extra-corpuscular (acquired)
    - Autoimmune hemolytic anemia
    - Isoimmune hemolytic anemia
  - *Mechanical injury:* Malaria, hemangioma, HUS
- **Increased blood loss**
  - *Acute:* Trauma, surgery, systemic disease
  - *Chronic:* Hook-worm infestation

HUS: Hemolytic uremic syndrome

TABLE 19.5: Broad etiological D/D anemia

	Nutritional	*Hemolytic*	*Aplastic*
Age of onset	> 3 months	Variable	Any
Risk factors	LSES, PEM	race/caste	–
Imp. history	Pica, worms	Transfusions	Infection/ drugs
Course	Gradual	Progressive	Acute
Appearance	FTT	Hemolytic face	–
HSmegaly	±	+++	–
Signs of bleeding	–	–	++
Jaundice	–	+	–
P. smear	*	**	Pancytopenia
Retic. count	N	↑↑	↓
Diagnosis	P. smear	Sp. tests	Marrow

LSES: Low socioeconomic status; **FTT:** Failure to thrive; **HSMegaly:** Hepatosplenomegaly
*Features may vary according to individual cause.
*Microcytic hypochromic or megaloblastic
**Marked anisocytosis poikilocytosis.

In addition, signs of excessive hemoglobin breakdown, e.g., icterus and gall stones, are common in chronic hemolytic anemia; while signs of pancytopenia, e.g. bleeding or recurrent infections indicate aplastic anemia.

Clinical evaluation of anemia aims to classify probable etiology in four major groups—(a) nutritional anemia, (b) hemolytic anemia, (c) aplastic anemia, and (d) hemorrhagic anemia, to limit the diagnostic workup **(Table 19.5)**.

- Important history in evaluation of anemia includes – (a) age of presentation, (b) family history, (c) dietary intake including early infant feeding, (d) chronic infection, diarrhea or worm infestation, (e) chronic systemic illnesses, e.g. renal or liver disease, (f) recent or recurrent bleeding including minor mucocutaneous bleeds, (g) blood transfusions, and (h) others, e.g. limb pains, hematuria, jaundice, etc. History of perinatal events is important in newborns and early infancy.
- Important examination findings in these cases include severity of anemia and presence of failure to thrive, hepatosplenomegaly, jaundice, bleeding, etc.

Anemia due to hemorrhagic causes is usually obvious, though concealed internal organ bleeding or occult blood loss, e.g. helminthiasis must be excluded by relevant investigations.

Chronic infections, e.g. malaria or tuberculosis are important causes of anemia in Indian children due to multiple causative factors, e.g. nutritional deficiency, hemolysis and bone marrow suppression.

Figure 19.2 provides a simplified algorithm for clinical differential diagnosis of anemia in children, as a starting point for investigations.

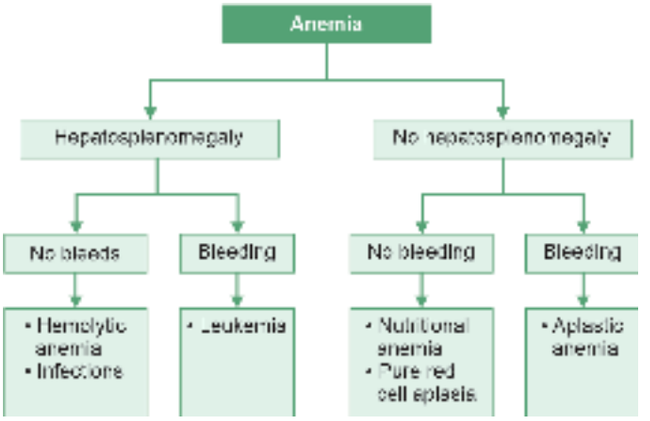

Fig. 19.2: Clinical approach to anemia.

Laboratory investigations in anemia may be divided into two broad groups—(a) *baseline investigations* to screen for possible etiology, and (b) *confirmatory tests*, depending on the suspected cause. Some baseline investigations are as follows:

- **Complete blood counts** to assess the severity of anemia (Hb%) and identify possible etiology, e.g. bone marrow depression or chronic infections/ inflammatory disorders.

  Assessment of RBC indices, i.e. mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular Hb concentration (MCHC) and red cell width (RDW) is very useful to limit diagnostic possibilities **(Table 19.6)**.

  – **MCV** (PCV/TRBC* × 10), normally ranges between 80–90 femtoliters (fl), except in early infancy (~108 fl at birth). According to MCV, anemia is classified as *microcytic*, *normocytic* or *macrocytic*.

  *(***PCV:** *Packed cell volume,* ***TRBC:*** *Total RBC count).*

TABLE 19.6: Morphological classification of anemia

- **Microcytic hypochromic**
  - Iron deficiency anemia*
  - Lead poisoning
  - Thalassemia trait
  - Pyridoxine deficient/dependent anemia
  - Sideroblastic/dyserythropoietic anemia*
  - Others" Copper deficiency,
- **Normocytic normochromic**
  - Aplastic hypoplastic anemia
  - Minor hemoglobinopathies or traits*
  - Acute/chronic blood loss
  - Chronic infections/Inflammations/renal disease
  - Auto-immune hemolytic anemia*
- **Megaloblastic**
  - Vitamin B_{12} deficiency*
  - Folic acid deficiency*
  - Myelodysplasia
  - *Others:* Liver disease, orotic aciduria

* with anisocytosis, i.e. increased RDW

- **MCH** (Hb/TRBC) normally range between 28–34 picograms/cell. According to MCH, anemia is classified as *normochromic* or *hypochromic.*
- **MCHC** (Hb/PCV × 100) normally ranges between 32–36 gm/dl. Hereditary spherocytosis is the commonest cause of elevated MCHC, but may also be seen in autoimmune haemolytic anemia or some hemoglobinopathies. It is reduced in iron deficiency.
- **RDW:** Major hemolytic and nutritional anemia are also associated with marked anisocytosis quantified by RBC distribution width *(RDW)*-a coefficient of variation in RBC size on electronic counters. Normal RDW is ~12–14%, which is increased in iron deficiency anemia (Low MCV), Hemoglobinopathies (normal/low MCV) or megaloblastic anemia (high MCV). Mentzer index (PCV/TRBC) is also interpreted similarly.

- **Peripheral smear (PS)** is an extremely valuable screening test in etiological diagnosis of anemia. A freshly prepared and stained (hematoxylin-eosin) smear should be examined not only for RBC morphology, e.g. shape, size, color and inclusion bodies, but also for leukocyte or platelet abnormalities to exclude leukemia and aplastic states.

  Normal RBC is a non-nucleated cell, which is biconcave in shape with central pallor. Common RBC abnormalities on smear include **(Fig. 19.3)**:
  - ***Abnormal size***, e.g. *microcytosis, macrocytosis* or *anisocytosis*, which should be confirmed by MCV and RDW values.
  - ***Abnormal shape***, e.g. *poikilocytosis* (variable shape) or irregular-shaped RBCs (*Schistocytes* or *Burr cells*) usually indicate hemolytic anemia due to any cause. Specific diagnosis of many hemolytic disorders, e.g. sickle cell anemia and RBC membrane defects, e.g. hereditary spherocytosis/elliptocytosis is possible on abnormal cell morphology.
  - ***Abnormal color,*** e.g. *hypochromia* (increased central pallor, occupying >1/3rd area) indicates iron deficiency while presence of *polychromasia* (irregular staining) or *target cells* (central pink area, surrounded by colorless zone and then rimmed by a pink border) suggests hemolysis. *Hyperchromia,* i.e. absence of central pallor, is caused by altered shape or thickness of RBC membranes and not due to higher Hb content.
  - ***Abnormal inclusion bodies*** within RBCs usually include *parasites*, e.g. malaria or kala-azar, *basophilic stippling*, i.e. small blue/black granules signs of lead poisoning and *Howell-Jolly bodies*, i.e. small round dark-blue remnant nucleus near the periphery of cell signs of asplenia, hyposplenism or splenectomy.
  - ***Presence of nucleated RBCs***, i.e. *normoblasts* indicate hemolytic anemia.

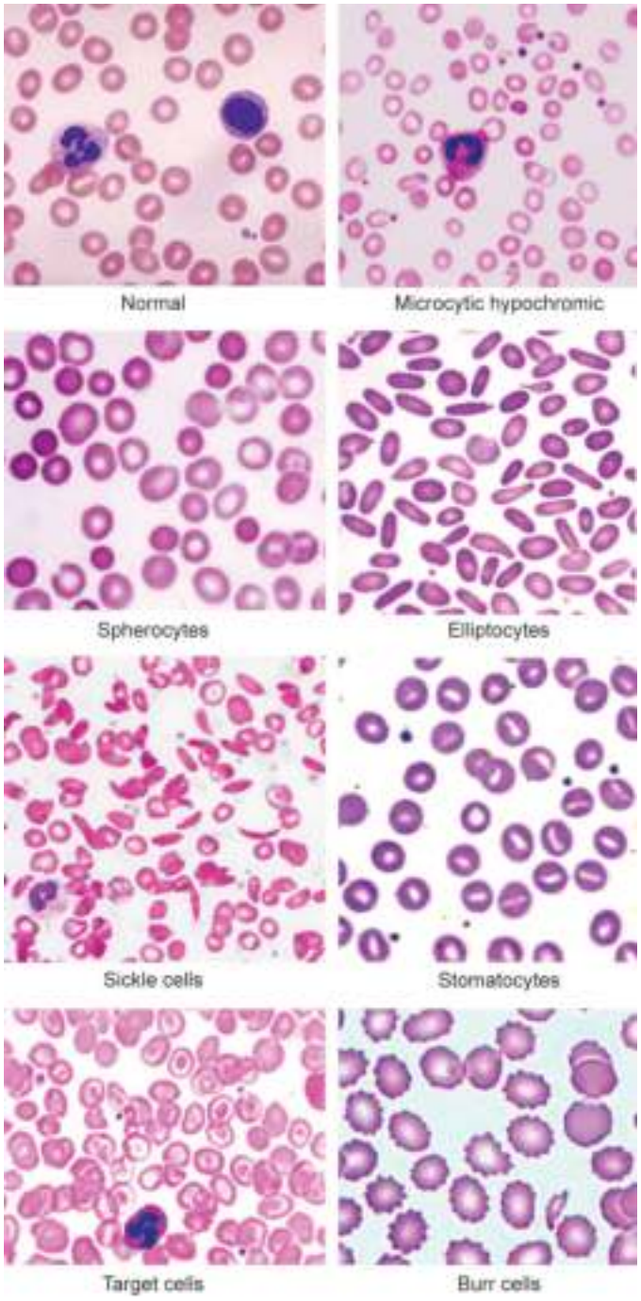

Fig. 19.3: Common peripheral smear abnormalities of RBCs.

- **Reticulocyte count:** Reticulocytes are immature RBCs, with spoked-wheel appearance on special *cresyl blue staining* of peripheral smear **(Fig. 19.4)**. Normal reticulocyte count does not exceed 2%, except at birth. *Reticulocyte production index* (RPI) or *corrected reticulocyte count* {Retic count × observed Hb/normal Hb × 0.5} is a better indicator of bone marrow activity. RPI of >3 is an indicator of rapid RBC turnover in hemolytic anemia, blood loss or iron therapy, while RPI of <2 indicates intrinsic bone marrow failure, e.g. aplastic anemia.

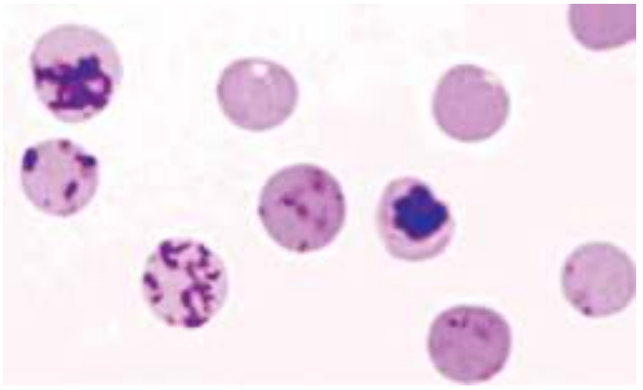

Fig. 19.4: **Reticulocytes.**

- **Biochemical tests,** e.g. iron studies or vitamin B_{12}/folate levels are indicated in assessment of nutritional anemia, while hemoglobin electrophoresis is required for suspected hemolytic anemia or unexplained anemia refractory to treatment. Other laboratory investigations are also required based on clinical suspicion, discussed in relevant chapters.
- **Bone marrow examination** is indicated in cases of suspected aplastic anemia or myeloinfiltrative disorders, e.g. leukemia, which should be examined for—(a) cellularity, (b) myeloid:erythroid ratio (N: 2–3:1), (c) parasites, and (d) abnormal stainings, specially for hemosiderin (for procedure *see* Ch 29.6). Hypocellular marrow with reduced M:E ratio indicates aplastic anemia while reverse indicates hyperactive marrow in hemolytic anemia.

19.3 PHYSIOLOGICAL ANEMIA OF INFANCY

Physiological anemia of infancy refers to *postnatal drop in Hb levels among normal children* due to developmental changes in rate of erythropoiesis and RBC destruction. In term infants, Hb levels fall gradually to reach their nadir (9–11 gm/dl) by 2–3 months, before rising again. This decline is more marked (7–9 gm/dl) and rapid in preterms, reaching the nadir by 3–6 weeks.

Etiopathogenesis: Normal newborns have higher Hb and Hct levels due to higher metabolic needs and lower oxygen tension in transplacental blood supply. Postnatally, these levels decline progressively due to many factors, including:

- Increased hemolysis due to shorter life-span of fetal RBCs as compared to adult RBCs.
- Decreased erythropoiesis due to:
  - Increased O_2 tension after initiation of '*self-breathing*' that inhibits erythropoietin activity;
  - Increased release of O_2 from adult RBCs, which have lesser O_2 affinity than fetal RBCs.
  - Shift of EPO production from liver to juxtaglomerular cells, which are relatively more sensitive to oxygen tension.

Clinically, physiological anemia in normal infants is usually mild and asymptomatic. *Exaggerated physiological anemia* is seen in: (a) preterms due to poor iron stores, (b) top-fed children due to poor assimilation of dietary iron, and (c) babies with perinatal blood loss, e.g. fetofetal transfusion and Rh-hemolytic disease.

Treatment: No treatment is necessary in most cases, as erythropoiesis resumes to desired rate soon after the nadir is reached. Physiological anemia is *unlikely to respond to iron or folic acid* supplements due to low EPO levels and hence, some cases of exaggerated physiological anemia may require blood transfusion.

Recombinant EPO therapy has been tried in some cases with equivocal benefits and usually unnecessary. However, *iron supplements should be started at 4–8 weeks in preterms and at 4 months in term infants to prevent iron deficiency anemia*.

19.4 NUTRITIONAL ANEMIA

Nutritional anemia is defined as the anemia *due to deficiency of one or more micronutrients required for normal erythropoiesis* and mainly includes: (a) iron deficiency anemia, and (b) megaloblastic anemia, due to vitamin B_{12} or folic acid deficiency.

19.4.1 IRON DEFICIENCY ANEMIA

Iron is the most important micronutrient in children, distributed in RBCs (60%), bone marrow, reticuloendothelial system (RES) and various iron-containing enzymes. Iron deficiency anemia (IDA) is the commonest cause of nutritional anemia, present in >50% of preschool and adolescent children.

Physiology: Fetus receives preferential delivery of iron transplacentally to build up body stores and maternal Hb status does not affect iron stores in baby unless she is severely anemic. However, as most of the transplacental transfer occurs in last trimester, preterms are more likely to have poor iron stores. Iron stores at birth are further enhanced by increased breakdown of RBCs in early postnatal life, and are sufficient for first 3–6 months of life.

Dietary requirements: While daily iron requirement is ~1 mg elemental iron/day, RDA varies from 6–12 mg/day in different age groups, as only <20% of ingested iron is actually absorbed.

Sources: Breast milk is the main source of iron in early infancy. Though iron content of human and animal milk is nearly same, absorption is 2–3 times more efficient from human milk and breast-fed babies are less likely to develop IDA than top-fed infants.

For older children, dietary iron is widely present as *heme form* in animal sources, e.g. meat, fish and poultry, or as *non-heme form* in green vegetables, pulses and jaggery.

Normal metabolism: Most of the dietary iron is in ferric form. Important steps in iron metabolism are as follows:

- ***Gastric digestion***, i.e. conversion of ingested ferric salts to ferrous form in presence of gastric acids, which is better absorbed than ferric form. Presence of *iron-binder*s, e.g. phosphates, phytates, oxalates in diet inhibits iron absorption, while lactose, vitamin C and certain amino acids enhance it.
- ***Intestinal absorption*** of iron at duodenum and upper jejunum by two energy-dependent processes: (a) mucosal uptake, and (b) transfer from mucosal cells to plasma. From mucosal cells, it is either delivered to plasma *or* remains stored as ferritin (after binding with a protein-*Apoferritin*), till these cells are shed in stools. Proportion of plasma transfer and mucosal storage depends on iron requirements of body. In IDA, most of the absorbed iron is delivered to plasma.
- ***Plasma transport:*** Absorbed iron in plasma is transported to bone marrow as bound form with *transferrin*a plasma protein, synthesized by liver. Transferrin receptors, present mainly on erythroid and hepatic cells, accept the iron from circulating iron-transferrin complex for further utilization. Percentage saturation of transferrin (total iron binding capacity or TIBC) is an important guide of iron state in body.
- ***Storage:*** Excess iron is stored in bone marrow and other reticuloendothelial (RES) tissues as *ferritin*, for future mobilization. In IDA, these stores are exhausted before the clinical appearance of anemia.
- ***Recycling:*** A part of the body iron is also produced by constant breakdown of hemoglobin in RES and stored in similar manner.

In brief, iron metabolism is regulated by: (a) *intrinsic factors*, i.e. body requirements, depending upon the rate of erythropoiesis and state of body stores, and (b) *extrinsic factors*, i.e. quality of consumed iron (ferrous vs. ferric form, presence of iron-binders or absorption-enhancers in diet, and state of intestinal mucosa.

In IDA, the iron deficiency is compensated by: (a) increased gut absorption, (b) enhanced bone marrow uptake from plasma, and (c) mobilization from stores.

Etiology: Common causes of IDA include:

- *Decreased iron stores*
  - Preterms/twin births
  - Delayed clamping of cord
  - Fetofetal or fetomaternal transfusion
- *Reduced dietary intake*
  - Top feeding
  - Delayed weaning
  - Improper dietary habits
- *Impaired absorption*
  - High phytate content in veg. diet
  - Achlorhydria/malabsorption syndrome
  - Malabsorption syndromes
- Excessive *blood loss*
  - *Occult:* Hookworms, Meckel's diverticulum
  - *External:* Trauma, surgery, bleeding diathesis
- *Higher requirements*
  - Preterms, adolescents and pregnancy
  - Recovery from malnutrition
- *Error in iron metabolism*
  - Idiopathic pulmonary hemosiderosis
  - Congenital transferrin deficiency
  - Sideroblastic anemia

Pathophysiology: Earliest event in IDA is excessive consumption of iron stores, which may be detected as reduced hemosiderin pigment in bone marrow many months before the actual fall in Hb levels. Important hematological changes in IDA, in sequence of their appearance are given in **Table 19.7**.

Clinical manifestations: IDA is most common in late infancy (6 months-2 years) and adolescence. Clinical spectrum varies according to the severity of deficiency, as follows:

- ***Mild or early IDA*** is characterized by *mental changes*, e.g. lack of attention span and irritability, due to impaired activity of iron-containing enzymes, e.g. monoamino oxide (MAO), cytochrome oxidase, etc. *Pica*-a behavioral problem, is frequently associated with IDA, though the cause-effect relationship is unclear.
- ***Moderate IDA*** presents with *visible pallor* of variable severity and features of *chronic hypoxia*, e.g. easy fatigability, anorexia, growth failure, etc. Mild splenomegaly and platynychia/koilonychia is common on examination.
- ***Severe IDA*** may be associated with *hemodynamic decompensation*, e.g. tachycardia, cardiomegaly, functional murmurs and even CCF.

Plummer-Vinson syndrome is a rare presentation of IDA with esophageal dysphagia (webs), koilonychia and splenomegaly.

Laboratory investigations in IDA include:

- ***Basic hematological work-up*** showing:
  - *Microcytic, hypochromic anemia on PS*
  - Low MCV, MCH, MCHC with high RDW (>14%)
  - Normal/slightly high reticulocyte count.

TABLE 19.7: Sequence of events in IDA

- Depletion of iron stores
- ↓ Serum ferritin levels
- ↑ Total iron binding capacity (TIBC)
- ↓ Hemoglobin levels
- ↓ Iron-containing enzymes activity
- Clinical pallor

- ***Biochemical investigations*** revealing:
  - Serum ferritin levels (<10 ng/ml)
  - Serum iron levels (<75 µg/dl)
  - TIBC (>470 µg/dl) with % saturation <16%
  - Free erythrocyte protoporphyrin (heme precursor) levels (>2.8 µg/g)

  Serum ferritin levels correlate well with total iron body stores, but may be falsely elevated or normal in acute inflammatory disorders despite low iron stores.
- ***Bone marrow exam***, though not routinely indicated, reveals hypercellularity with erythroid hyperplasia and *absence of hemosiderin* on Prussian blue staining.
- ***Ancillary investigations***, e.g. stool exam for occult blood/parasites, to search for primary cause.

D/D of IDA includes other causes of *microcytic hypochromic anemia*, i.e. (a) chronic lead poisoning (basophilic stippling of RBCs), (b) thalassemia trait (normal RDW and raised HbA_2), (c) sideroblastic anemias, and (d) rare causes, e.g. congenital atransferrinemia.

Management includes correction of anemia and treatment of primary cause, e.g. worm infestations. Modalities to correct the anemia depend on its severity and include:

- **Oral iron therapy** is the treatment of choice in most cases, given as ferrous salts (PO 3–6 mg/kg/d q8–12hr on empty stomach) for 2–3 months *or* at least 8 weeks after Hb returns to normal. Many oral preparations are available containing heme *or* different ferrous salts, each with variable content of elemental iron. Anhydrous ferrous sulfate is the richest source of elemental iron (37%), followed by fumarate (33%), succinate (23%) and gluconate salts (20%).

  Iron absorption may be enhanced by—(i) avoiding concomitant intake of meals/milk, and (ii) additional vitamin C supplementation (50 mg/kg).

  Common side-effects of iron therapy include GIT upsets, e.g. diarrhea/constipation (which can managed by change of iron salt) and blackish staining of teeth.

  Response to therapy may be monitored by assessing the sequence of recovery events **(Table 19.8)**.

  Therapeutic failure to oral iron therapy indicates: (a) continued blood loss, (b) improper preparation/dose/compliance, (c) high phosphate diet, (d) associated megaloblastic (Dimorphic) or/hemolytic anemia, and (e) presence of chronic illnesses/infection, and (f) congenital causes, e.g. sideroblastic anemia.
- **Parenteral (intravenous) iron therapy** is rarely required in children with: (a) intolerance to oral therapy, (b) severe malabsorption states, e.g. inflammatory bowel diseases, (c) severe or ongoing blood losses at a rate too rapid for oral intake to compensate, e.g. in coagulation disorders, menorrhagia, etc., and (d) dialysis or chemotherapy, along with EPO to ensure adequate iron supply, etc..
  - ***Dose*** of parenteral iron can be calculated by *Ganzoni* formula, as:

    Iron (mg) = Wt in kg x Hb deficit x 2.4 + (15 x Wt in kg)

    where Hb deficit is (Target Hb – actual Hb in mg/dl), 2.4 is the constant derived by multiplying blood volume (0.7 L/kg) with 3.4 (iron content/gm Hb) and 15 mg/kg is the iron required to replace stores.

    Total calculated dose must be given over 3–7 days, diluted with equal volume of normal saline and infused slowly as 100 mg/30 minutes. Total daily dose should not exceed 7 mg/kg/day (max 300 mg) to minimize side effects, test dose is not necessary in children above 1 month of age.
  - ***Formulations:*** Many parenteral formulations as iron-carbohydrate complex are available with variable elemental iron concentrations and immunogenic potential. Preferred option is ferric carboxymaltose (50 mg iron/ml), which can be safely administered as 15 mg/kg (Max 1000 mg) over 15–20 minutes with minimal risk of hypersensitivity reactions. Iron-sucrose maltose is frequently used in children with advanced renal disease, given as 1 mg/kg per session of dialysis followed by 1–2 mg/kg/week, diluted in 150 ml of normal saline and infused slowly over 30–90 minutes.
  - ***Side effects*** of parental iron include infusion-related reactions such as flushing, headache, muscle/joint pain, nausea, rashes, fever, chills and very rarely, anaphylaxis.
  - ***Contraindications*** include hypersensitivity to previous parenteral dose, when even the alternative formulation must be used cautiously.
- **Blood transfusion** is recommended only in very severe anemia (<5 gm/dl), given as packed cells (10 ml/kg) with monitoring for fluid overload, which may be prevented by pre-/post-transfusion furosemide. In very severe anemia with CCF, transfusion should be given very slowly, not exceeding 5 ml/kg/sitting, or preferably as exchange transfusion.

Prevention for IDA include: (a) promotion of breast-feeding, (b) increased consumption of iron-rich foods, e.g. beans, green leafy vegetables, jaggery, ragi, etc.,

TABLE 19.8: Time table of clinico-hematological response after initiation of iron therapy

Time period	*Clinical/hematological response*
12–24 hour	↓ irritability, ↑ appetite/attention span*
36–48 hour	Bone marrow hyperplasia
48–72 hour	Increase in reticulocyte count
4–30 days	Rise in Hb levels (0.4 gm/dl/day)
1–3 months	Replacement of stores

*due to replacement of enzymatic iron

(c) routine iron supplements in early infancy and adolescence, and (d) early diagnosis and treatment of cause, e.g. hookworms.

National Iron Plus Initiative (NIPI) Programme

National Iron Plus Initiative 2013 is the current version of previous National Nutritional Anemia Prophylaxis Programme (1970) and National Nutritional Anemia Control Programme (1995), presently administered as a component of *Reproductive Maternal, Newborn, Child and Adolescent (RMNCH+A) strategy* under National Health Mission.

Major interventions under NIPI, with reference to children include:

- *Prevention of anemia* in non-anemic children with prophylactic IFA supplements, as follows:
  - 6–59 mo : 20 mg + 100 µg biweekly
  - 5–10 yrs : 45 mg + 400 µg weekly
  - 10–19 yrs : 100 mg + 500 µg weekly
- *Treatment of mild to moderate anemia* in anemic children with iron therapy as follows:
  - 6–59 mo (Hb <10.9 gm/dl): 3 mg/kg/d for 2 mo
  - 5–10 yrs (Hb <11.5 gm/dl) : 3 mg/kg/d for 2 mo
  - 10–19 yrs (Hb <11.9 gm/dl) : 60 mg/d for 3 mo
- Referral of children with severe anemia, i.e. Hb <7 gm/dl below 5 years of age and <8 mg in older children, to nearest district hospital or first referral unit.

NIPI also provides IFA supplements (100 mg+500 µg) to pregnant women for 100 days after first trimester, to lactating mothers for 100 days in postpartum period and to all reproductive age (15–45 years) women once a week throughout the year. It also has provisions and guidelines for treatment of anemia in pregnant and lactating women.

Anemia Mukt Bharat

"*Anemia Mukt Bharat*" is a component of Poshan Abhiyaan, launched in 2018 to provide holistic nourishment. It aims to reduce the prevalence of anemia by 3% points per year in children, adolescents and reproductive age women, using a 6x6x6 strategy, i.e. 6 beneficiaries, 6 interventions and 6 institutional mechanisms.

- *Six beneficiaries* include: (1) children 6–59 months; (2) children 5–9 years, (3) Adolescents 10–19 years, (4) reproductive age women (20–24 years), (5) pregnant women and (6) lactating mothers.
- *Six interventions* include: (1) prophylactic IFA supplementation as in NIPI, (2) periodic 6-monthly deworming with oral albendazole for children 1–19 years, (3) behavioral change campaign including to promote delayed cord clamping, (4) digital testing of anemia and point-of-care treatment, (5) iron fortified foods in public health programs, and (6) linkage with endemic diseases, e.g. malaria, hemoglobinopathies, etc.

19.4.2 MEGALOBLASTIC ANEMIA

Megaloblastic anemia is a hematological term to describe anemia with presence of characteristic *megaloblasts* in peripheral smear, i.e. large RBCs with finely dispersed nuclear chromatin and disproportionate maturation of nucleus and cytoplasm **(Fig. 19.5)**.

It is commonly caused by deficiency of two essential co-factors for synthesis of nucleic acids-*vitamin B_{12}* and *folic acid*. Rare causes include thiamine deficiency/dependency states and inborn errors of nucleic acid metabolism, e.g. Orotic aciduria and Lesch-Nyhan syndrome.

Peripheral smear in megaloblastic anemia, irrespective of the etiology, characteristically shows:

- Macrocytic RBCs (MCV>110 fl) with immature erythroid cells;
- Presence of megaloblasts
- Hypersegmented polymorphs with neutropenia,
- Thrombocytopenia of variable severity

Folic acid deficiency: Normal folic acid requirement in children is ~100 µg/day; supplied adequately as folates in most foods and milk (except goat/camel milk). It is absorbed throughout the intestines (Ch 6.3).

Etiology: Folic acid deficiency rarely dietary, usually seen in cases with:

- *Poor absorption:* Malabsorption syndrome, specially Fish-tapeworm *(D. latum)* infestations.
- *Increased requirements*, e.g. hemolytic anemia.
- *Impaired folate metabolism* due to drugs, e.g. methotrexate, pyrimethamine, and phenytoin.
- *Dietary deficiency* in babies fed on goat, camel or unfortified powder milk.

Clinically, most cases present at 4–7 months of age with:

- Progressively developing chronic anemia.
- Failure to thrive and chronic diarrhea.

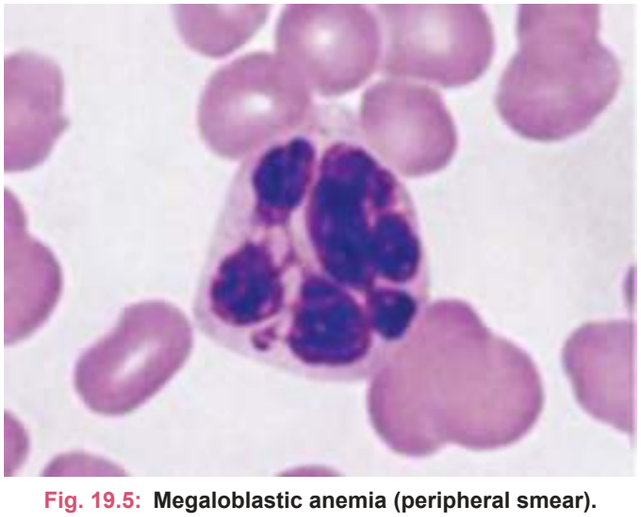

Fig. 19.5: **Megaloblastic anemia (peripheral smear).**

- *Neurological features*, e.g. tremors and developmental regression.
- *Hyperpigmentation* over dorsum of fingers/thigh.
- *Bleeding* in severe cases due to thrombocytopenia.

A combination of megaloblastic anemia, neurological signs and cutaneous hyperpigmentation suggests possibility of infantile tremor syndrome (Ch 18.7).

Diagnosis is established by:

- Megaloblastic peripheral smear,
- Low serum folate levels <3 ng/ml (N: 5–20 ng/ml),
- ***FIGLU test***, i.e. excretion of *formiminoglutamic acid* in urine after loading with histamine.

Management involves oral *or* parenteral folic acid therapy (1–5 mg/day for 3–4 weeks), along with vitamin B_{12} supplements (1000 µg/day). Isolated folic acid therapy without B_{12}, may worsen neurological problems associated with co-existing vitamin B_{12} deficiency despite correction of anemia.

Vitamin B_{12} deficiency: Daily requirement of vitamin B_{12} is very low (~1–5 mg), which can be easily fulfilled by dietary *cobalamin* – vitamin B_{12} precursor, present in almost all foods. Vitamin B_{12} absorption requires its hydrolysis by gastric acid and combination with a specific protein — *intrinsic factor of Castle (IFc)* present in stomach. It is mainly absorbed in *distal ileum* and transported in plasma as bounded form with a protein-*transcobalamin*.

Etiology: Dietary deficiency is extremely rare except in total vegans and important causes of Vitamin B_{12} deficiency in children include:

- Congenital IFc deficiency (*juvenile pernicious anemia*),
- Malabsorption syndromes involving terminal ileum,
- IFc-B_{12} receptor deficiency (*imerslund syndrome*)
- Congenital transcobalamin deficiency

Achlorhydria *and* presence of Ifc antibodies are other important causes of vitamin B_{12} deficiency in adults.

Clinically, *juvenile pernicious anemia*-a rare autosomal recessive disorder of Ifc deficiency, is the prototype of vitamin B_{12} deficiency, which usually presents at 9–12 months of age, with a triad of:

- Progressively severe anemia,
- Glossitis, i.e. red smooth and painful tongue, and
- CNS signs, e.g. ataxia, paresthesia, hypo/hyperreflexia.

Vitamin B_{12} deficiency due to other causes presents similarly, except differences in age of presentation and severity.

Diagnosis is established by:

- Megaloblastic peripheral smear,
- Low S. vitamin B_{12} levels < 100 pg/ml,
- Urinary excretion of *methylmalonic acid* (>3.5 mg/d)
- Schilling test.

Schilling test is used to establish presence of vitamin B12 deficiency (Part I) as well as to differentiate between IFc deficiency and malabsorption defects (Part II).

In the *first part of test*, a small amount of radiotagged (^{57}CO) vitamin B_{12} is given orally, followed by a flushing dose of 1 mg parenteral vitamin B_{12} after 2 hours, which leads to excretion of >10–30% of radio-tagged dose in urine. Excretion of <2% of radio-tagged vitamin B_{12} indicates its retention in body, due to vitamin B_{12} deficiency.

In the *second part*, test is repeated with 30 mg of IFc, given along with the radio-tagged dose. Correction of test results indicates IFc deficiency, while persistent abnormality suggests malabsorption.

Management depends on severity of disease, and generally includes parenteral vitamin B_{12} (IV/IM) 250–1000 µg/day for 2 weeks, then weekly for next 2–3 months, and then monthly doses till correction of anemia. Lower range of dose (0.2 mg) may be used in infants and young children.

Life-long therapy is required in juvenile pernicious anemia or malabsorption disorders. Children with neurological signs must receive parenteral vitamin B_{12} 1000 µg (1 mg) daily for 2 weeks followed by alternate week for 6 months and then monthly for life.

Prevention with prophylactic vitamin B_{12} is advised in cases with malabsorptive states, e.g. autoimmune gastritis or ileal resection.

19.5 HEMOLYTIC ANEMIA

Normal life span of RBCs is ~120 days, except a shorter span ~60–90 days in newborns. Every day, ~1% of senescent RBCs are removed from circulation and replaced by new cells from bone marrow. All hemolytic anemias **(Table 19.9)** are characterized by decreased life span of RBCs with resultant rapid turn-over.

General pathophysiology: Rapid turn-over of RBCs in hemolytic anemia requires—(a) elimination of degradation products, and (b) compensatory increase in erythropoiesis. Bone marrow is capable to increase its output as much as by 2–3 times in acute stress and 6–8 times following chronic stress. Further increase in erythropoietic requirements necessitates reactivation of extra-medullary sites including other marrow sites, liver and spleen.

Severity of anemia in hemolytic disorders depends on severity of hemolysis as well as adequacy of compensatory erythropoiesis. However, even well compensated cases are susceptible for intermittent life-threatening aplastic crisis, usually precipitated by parvoviral infections.

General clinical picture of typical hemolytic anemia is dominated by signs of:

- Progressively severe pallor with/without intermittent exacerbations.

TABLE 19.9: Classification of hemolytic anemia

- **Congenital**
  - ***RBC membrane defects***
    - Hereditary spherocytosis (commonest)
    - *Others:* H. elliptocytosis, stomatocytosis
    - Paroxysmal nocturnal hemoglobinuria
  - ***RBC enzyme defects***
    - *HMP pathway:* G6PD deficiency
    - *Glycolytic pathway:* Pyruvate kinase deficiency
  - ***Hemoglobinopathies***
    - *Deficient HbA synthesis:* Thalassemia
    - *Abnormal Hb:* Sickle cell anemia, Hb-C, D, E
    - *Mixed hemoglobinopathies:* Sickle thalassemia
- **Acquired**
  - ***Immunological RBC injury***
    - *Iso-immunization:* HDN, mismatch transfusion
    - Autoimmune hemolytic anemia
  - ***Mechanical RBC injury***
    - *Direct:* Malaria, infections
    - *Sequestration:* HUS, AV malformations
  - ***Toxic or metabolic RBC injury***
    - Acute hepatic/renal failure
    - Insect/snake bites, etc.

HUS: Hemocytic uremic syndrome; **HMP:** Hexose monophosphate; **HDN:** Hemolytic disease of newborn

- Compensatory erythropoiesis, e.g. hepatosplenomegaly, hemolytic facies and pathological fractures due to expansion of bone marrow.
- Excessive heme degradation, e.g. icterus, gallstones, hemosiderosis, etc.

General hematological picture in hemolytic anemia is characterized by:

- Progressive drop in Hb with/without intermittent exacerbations
- High reticulocyte count due to rapid RBC turnover, appearance of immature RBCs, e.g. normoblasts, in peripheral smear along with marked anisocytosis, poikilocytosis, polychromasia and target cells, etc.
- Hypercellular bone marrow with high M:E ratio.
- Reduced survival time of radiotagged (^{51}Cr) RBCs.
- Elevated levels of Hb degradation products, e.g. unconjugated bilirubin, iron and haptoglobins.

Some common hemolytic anemias are discussed in this chapter with greater details along with salient features of other important but uncommon disorders.

19.5.1 HEREDITARY SPHEROCYTOSIS

Hereditary spherocytosis is the commonest intrinsic red cell membrane defect and fourth common cause of hemolytic anemia in childhood.

Etiology: Hereditary spherocytosis is predominantly an autosomal dominant disorder (~75%), characterized by a molecular defect in two RBC stromal proteins-*spectrin* and *ankyrin*. These abnormal stromal proteins increase cation permeability of cell membranes with resultant ballooning of RBCs (spherocytes), which are then trapped and rapidly destroyed in splenic sinuses.

Clinical manifestations vary according to the severity of defect, with most severe cases presenting with neonatal hyperbilirubinemia, requiring phototherapy or exchange transfusion.

However, most cases presents in *early infancy* with a clinical triad of—(i) mild/moderate pallor, (ii) progressively severe splenomegaly, and (iii) persistent jaundice. Despite gross splenomegaly, anemia in hereditary spherocytosis is rarely severe enough to require transfusions except during intermittent *aplastic crisis*, often precipitated by viral (parvovirus) infections.

Formation of gallstones due to excessive bilirubin excretion, is a major complication of hereditary spherocytosis, seen in ~50% of older children/adults.

Laboratory diagnosis is based on:

- *Presence of spherocytes* in peripheral smear, i.e. small, round or biconvex RBCs with absent or reduced central pallor **(Fig. 19.3)**.
- *Osmotic fragility test*, i.e. increased osmotic fragility on incubation of RBCs in progressive dilutions of normal saline. In doubtful cases, prior incubation of RBCs at 37°C for 24 hours (*modified osmotic fragility test*) accentuates this fragility.
- *Demonstration of specific protein defect* by Gel electrophoresis/densitometric studies and RBC membrane studies are confirmative.

Other important laboratory abnormalities include: (a) moderate anemia (8–10 gm/dl) with low MCV but *high* MCHC, (b) high reticulocyte count (~ 5–20%), (c) indirect hyperbilirubinemia, (d) hypercellular bone marrow with erythroid hyperplasia (rarely needed), and (e) presence of gallstones on USG, which is indicated in all cases of hereditary spherocytosis with abdominal pain.

D/D includes other causes of spherocytes in peripheral smear, e.g. (a) Rh-hemolytic disease in newborn, (b) autoimmune hemolytic anemia, (c) Wilson disease, (d) burns, and (e) septicemia.

Management: Since anemia in hereditary spherocytosis is mainly due to increased trapping and destruction of RBCs in the spleen, total or partial *splenectomy is the treatment of choice*. However, it is indicated only in cases with—(a) gross splenomegaly, (b) persistent moderate anemia <8 gm/dl, or (c) recurrent aplastic crisis. While peripheral smear abnormalities persist even after splenectomy, Hb levels usually return to normal. Splenectomy also reduces the risk of traumatic rupture of spleen.

Splenectomy should preferably be deferred till 5–6 years of age to cross the vulnerable age for infections. Till then, contact sports should be avoided to minimize risk of splenic injury. Preventive vaccines against

capsular organisms (pneumococcal, *H. influenzae* B and meningococcal) along with oral penicillin prophylaxis are recommended in splenectomized children.

Other interventions include blood transfusions during aplastic crisis, folic acid supplements (PO 1 mg/day), and treatment of complications, e.g. gallstones.

Other uncommon RBC membrane defects include:

Hereditary elliptocytosis/stomatocytosis may be either asymptomatic or present with mild hemolytic anemia. Diagnosis is established on smear examination. No treatment is necessary in asymptomatic cases, though symptomatic cases may require splenectomy and folic acid supplementation.

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare and RBC membrane defect, which renders them susceptible to damage by serum complement.

Clinically, these cases present with: (a) chronic hemolytic anemia with mild pancytopenia, (b) intermittent nocturnal paroxysms of intravascular hemolysis with hemoglobinuria, and (c) secondary complications, e.g. thromboembolic episodes, aplastic anemia and leukemia.

Diagnosis usually rests on detection of hemosiderinuria during attacks and a positive *Ham (acid serum) test* or *sucrose-lysis test*, suggestive of complement lysis. Flow cytometry to detect deficiency of glycolipid-bound membrane proteins, identified by CD_{59} expression, is currently the best diagnostic test for PNH.

Management includes: (a) glucocorticoids during acute hemolytic episodes, (b) prolonged anticoagulant therapy in thromboembolic episodes, and (c) bone marrow stimulants, e.g. ATG, cyclosporin, androgens, erythropoietin and GM-CSF, etc. Bone marrow transplant has been attempted in few cases as curative therapy.

19.5.2 G6PD DEFICIENCY ANEMIA

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the commonest RBC enzymopathy, usually presenting as severe hemolysis after exposure to oxidizing drugs or substances **(Table 19.10)**.

Etiopathogenesis: Since RBCs do not contain mitochondria, glucose is largely metabolized in them by two anaerobic pathways – 90% by Embden-Meyerhof pump (EMP) and 10% by hexose monophosphate shunt (HMS).

G6PD is the most important enzyme of HMS pathway that has an important function to maintain glutathione-an antioxidant intracellular enzyme, in its reduced state (GSH). In G6PD deficiency, reduced GSH activity with accumulation of intracellular oxidants leads to increased RBC membrane permeability and denaturation of hemoglobin to form intracellular *Heinz bodies*.

These abnormal RBCs are then trapped and destroyed in the spleen, producing hemolysis. Over 100 isoenzymes of G6PD with variable activity have been identified, commonest being G6PD B^+ or A^+ in normal population and G6PD A^- or B^- mutant enzymes with reduced activity in affected population.

G6PD deficiency is an *X-linked recessive* disorder with incomplete dominant expression. Affected cases, instead of having normal isoenzyme variants, possess mutant variants with lower activity, i.e. G6PD B^- or G6PD A^-.

Epidemiology: G6PD B^- variant is the commonest cause of G6PD deficiency in Indian population, being more prevalent in jews and in north-west region. Being an X-linked recessive disease, clinical manifestations are almost always seen only in males. However, even heterozygous females, though asymptomatic, have intermediate enzyme activity due to random gene inactivation (*Lyon's hypothesis*).

Clinically, G6PD deficiency may present in three distinct forms, depending on the type of enzyme variant, severity of deficiency and the nature/amount of oxidant exposure.

- *Mildest form* presents with transient hemolysis only after exposure to strong oxidants, e.g. primaquine. Hemolysis abates after some time even if the offending drug is continued and neonatal hyperbilirubinemia is not seen.
- *Commonest form* in Indian children with G6PD B variant presents with moderate to severe hemolytic episodes after exposure to oxidant substances. Hemolysis continues till the drug is stopped. These episodes present with sudden hemoglobinuria (red-colored urine), rapidly progressive pallor and hemodynamic collapse. Some cases may present with neonatal hyperbilirubinemia.
- *Severe cases* present with chronic non-spherocytic hemolytic anemia and splenomegaly due to persistent hemolysis even without oxidant exposure. Neonatal hyperbilirubinemia is common.

Diagnosis depends on:

- Classic clinical presentation with acute hemolytic episodes after exposure to an oxidant drug.
- Presence of intracellular *Heinz bodies* on supravital staining of RBCs. Heinz bodies are not visible after 3–4 days of hemolysis, as cells containing these bodies are rapidly cleared by spleen.
- *Quantitative G6PD activity* estimation should be deferred for at least 3 weeks of hemolytic episode, as immediate results may be misleading due to

TABLE 19.10: Precipitating oxidants in G6PD deficiency

- ***Drugs:***
  - *Antimalarials:* Primaquine, quinine
  - *Antibacterials:* Sulfonamides, nalidixic acid
  - *Others:* Vitamin K analogs, aspirin, methylene blue
- ***Chemicals:*** Naphthalene balls, benzene
- ***Illness:*** Viral fevers, hepatitis, diabetic ketoacidosis
- ***Others:*** Fava beans (a Mediterranean dietary staple)

preponderance of reticulocytes and younger RBCs in circulation after severe hemolysis, which have significantly higher G6PD activity.

Management is only supportive and includes:

- Immediate stoppage of offending drug.
- Alkalization of urine with IV/PO $NaHCO_3$ to prevent precipitation of acid hematin in renal tubules and consequent renal failure.
- Correction of fluid and electrolyte imbalance
- Blood transfusion in severe cases.

Prevention of further episodes in known G6PD deficient children is vital. Their case-papers should prominently mention the diagnosis to avoid future exposure with oxidant drugs. In high-risk communities, it is advisable to test G6PD activity before administering oxidant drugs, e.g. primaquine or sulfonamides.

Other uncommon enzyme defects include:

Pyruvate kinase deficiency is an autosomal recessive disorder of EMP pathway — main energy pathway in RBCs. Low ATP production in these cases adversely affects cellular functions and pliability, decreasing their life-span. Heterozygous children have moderate reduction in pyruvate kinase activity.

Clinical presentation varies from severe neonatal hyperbilirubinemia to mild/moderate persistent hemolysis in later life with variably severe anemia, persistent jaundice and splenomegaly.

Diagnosis rests on low pyruvate kinase levels in RBCs with normal osmotic fragility (d/d hereditary spherocytosis).

Management includes folic acid supplements and splenectomy in severe cases. Transfusion is rarely needed.

Methemoglobinemia: Methemoglobin is characterized by presence of heme iron in ferric (F^{+++}) form, instead of ferrous (Fe^{++}) form in hemoglobin, which renders it non-functional and imparts a brown color to the blood.

In normal individuals, methemoglobin contributes <2% of total Hb. Methemoglobinemia represents an imbalance in normal process of oxidation and reduction of heme iron, leading to increased methemoglobin concentration.

Etiologically, methemoglobinemia is either an autosomal dominant hemoglobin disorder (*Hb-M disease)* or an autosomal recessive enzymopathy (*cytochrome B-5 reductase deficiency).*

Clinically HbM disease presents with persistent central cyanosis due to abnormal color of methemoglobin since birth, without respiratory distress. However, children with enzymopathy are apparently normal till exposed to strong oxidants **(Table 19.10)**, when they present with sudden appearance of cyanosis and mild respiratory distress. Cyanosis appears only when methemoglobin levels exceed 15%.

Diagnosis must be suspected in deeply cyanosed cases with minimal respiratory distress and *chocolate-brown color* of blood sample, confirmed on Hb electrophoresis.

Management of these cases includes:

- *IV Methylene blue* (1–2 mg/kg) to eliminate acute cyanosis in enzymopathy, followed by oral maintenance therapy (3–5 mg/kg/day).
- *Vitamin C supplements* (PO 200–500 mg/d q8–12hr) to reduce methemoglobin concentration <10% (and cyanosis), till therapy is continued.

Prevention of attacks involve avoidance of exposure to oxidant drugs/chemicals including naphthalene balls, nitrobenzene products like shoe-polish, perfumes, etc.

19.5.3 THALASSEMIA

Thalassemia is the commonest hemoglobinopathy in India, with reported carrier rate ranging from 3–17% in different communities, more common in Sindhi, Kacchi, Lohanas, Punjabis, Bengalis and Gujaratis.

Term *thalassemic syndromes* denotes a group of heterogeneous disorders, all characterized by inadequate or no synthesis of the normal adult hemoglobin (HbA).

Genetically, thalassemia is an autosomal recessive disorder with over 200 known mutations in globin genes, leading to either absent or inadequate synthesis of the globin chains in adult hemoglobin (HbA).

Depending on the defective globin gene, thalassemia may be broadly classified as α-*thalassemia* or β-*thalassemia*.

Defective production of globin chains leads to: (a) absence or reduced levels of HbA, (b) increased levels of abnormal hemoglobins, e.g. HbF, and (c) accumulation of normally produced globin chains (e.g. α chains in β thalassemia) in absence of complementary globin chains; all contributing to decreased life span of RBCs.

β-thalassemia, the commonest of thalassemic syndromes, is characterized by total or partial deletions of β-globin genes, leading to total (β^0) or partial (β^+) failure in β-chain production as follows:

- Homozygous state with complete absence of β-chain production (β/β) with complete absence of HbA, referred as ***thalassemia major*** or *Cooley's anemia or* transfusion-dependent thalassemia;
- Homozygous state with partial depression of β-chain production ($\beta^+/^+$) and marked reduction (but not complete absence) in HbA levels, termed as ***thalassemia intermedia***, or non-transfusion-dependent thalassemia.
- Heterozygous (carrier) state with complete suppression of β-chain production in only one of the β genes (β/β), *referred as* ***thalassemia minor.***
- Heterozygous (carrier) state with partial suppression of only one of the β genes (β/β^+), *referred as* ***thalassemia trait.***

Hematologically, deficient β-chain and adult Hb production is partly compensated by increased levels of HbF, which does not contain β chains. However, HbF has higher affinity to oxygen and does not release it in tissues as efficiently as HbA, leading to a state *of persistent tissue hypoxia*, apart from reduced life span of RBCs.

Clinical presentation: Severity of the hemolytic process in thalassemia depends on the percentage of HbA in the affected child and divided into three categories, i.e. thalassemia major, thalassemia intermedia or thalassemia minor.

Thalassemia major *(Cooley's anemia, transfusion-dependent thalassemia)* presents with:

- Progressively severe hemolytic anemia, usually from 2–6 months of life, requiring repeated blood transfusion to maintain sustainable Hb levels.
- Signs of chronic hypoxia, e.g. effort intolerance, pallor, growth failure and CCF in severe cases.
- Signs of increased hemolysis, e.g. progressive hepatosplenomegaly, hemolytic jaundice, and gallstones in older children.
- Signs of tissue iron excess (hemosiderosis) due to increased Hb breakdown, e.g. hyperpigmented skin, diabetes mellitus and cardiomyopathy.
- Signs of compensatory erythropoiesis in bone marrow and extramedullary sites, e.g. hemolytic face, hepatomegaly and pathological fractures.

Hemolytic facies, usually seen after 2–3 years of age, is characterized by: (a) prominent forehead and malar eminences due to extramedullary expansion, (b) wide separation of teeth due to maxillary hypertrophy, and (c) an ash-white complexion due to combination of pallor, hemosiderosis and jaundice **(Fig. 19.6)**.

Thalassemia intermedia *(non-transfusion dependant thalassemia)* presents usually beyond infancy with relatively moderate hepatosplenomegaly and less transfusion requirements than in thalassemia major.

TABLE 19.11: Electrophoretic patterns in thalassemia

	HbA	*HbF*	HbA_2
Normal ($\alpha_2\beta_2$)	90–98	2–3	2–3
T. major (β°/β° or β^+)	Nil	> 90	> 3.4
T. intermedia (β^+/β^+)	0–40	60–80	Normal
T. Minor or trait (β/β° or β^+)	90–95	2–10	5–7

All values in % of total Hb

Thalassemia minor is generally asymptomatic except mild microcytic hypochromic anemia, minimal splenomegaly and no need for transfusions.

Laboratory diagnosis of thalassemia may be divided into three categories:

- **Confirmatory diagnosis** with Hb electrophoresis or HPLC (high performance liquid chromatography) to identify abnormal electrophoretic patterns, depending on the type of thalassemia **(Table 19.11)**.
- **Genetic studies** of index case as well as both parents in confirmed cases to assess the risk of recurrence and parental counseling. Risk of recurrence is 25% for thalassemia major and 50% for thalassemia trait in case of both parents being carriers, with 25% chance of having an unaffected child.
- **Supportive investigations,** for evidence of:
  - *Hemolysis, i.e.* microcytic hypochromic picture of PS, with anisopoikilocytosis, polychromasia and normoblasts.
  - *Iron overload, i.e.* elevated serum iron and ferritin levels, low TIBC and excess hemosiderin deposits in bone marrow.
  - *Secondary organ dysfunction*
  - *Compensatory hematopoiesis* with hypercellular bone marrow and erythroid hyperplasia.
  - *Extramedullary erythropoiesis* in older children with thalassemia major, e.g. (a) *hair-on-end appearance or* crew-cut appearance on skull X-ray with wide diploic space and prominent trabeculae **(Fig. 19.7)**,

Fig. 19.6: Hemolytic face: (A) Front view; (B) Side view.

Fig. 19.7: Hair end-on appearance on skull X-ray.

and (b) rectangular thickening of metacarpals and phalangeal bones.

Excessive hemolysis may also lead to elevated serum bilirubin and urinary urobilinogen levels.

Antenatal diagnosis is possible by *chorionic villous sampling* for genetic studies at 10–13 weeks weeks or by *fetal blood sampling* for HPLC/electrophoresis at 16–20 weeks.

Management of thalassemia aims to (a) maintain optimal Hb levels by repeated blood transfusions to minimize hypoxic damage, prevent marrow expansion and ensure normal growth; (b) prevent iron toxicity due to increased hemolysis and repeated transfusions by chelation therapy; (c) reduce the rate of hemolysis by splenectomy, if necessary, (d) monitor and manage secondary organ dysfunctions including endocrinal complications, and (e) ultimately, to cure the child with bone marrow transplant and gene therapy. Some important aspects of management are as follows:

a. Transfusion therapy: Repeated blood transfusions to maintain an Hb level at ~10 gm/dl, is the mainstay of treatment in T. major. Super transfusion to maintain Hb levels >12 gm/dl is no longer recommended due to higher iron overload.

Most cases require 15–20 ml/kg of packed cell transfusions every 4–5 weeks, which may be given on day care basis. Transfusions should be started as early as possible to prevent expansion of bone marrow and splenomegaly. To avoid transfusion reactions, freshly separated, properly-matched and triple-filtered (to remove granulocytes and plasma proteins) packed cells should be used, along with careful monitoring for transfusion reactions and use of diuretics to avoid overload. Hepatitis B vaccine is advisable in all cases. While transfusion requirements gradually increase with age, sudden increase in transfusion requirements must be investigated for possibility of hypersplenism *or* aplastic crises.

Newer transfusion modalities include transfusion of specially separated younger cells, i.e. neocytes with longer life span and removal of gerocytes (older cells) by plasmapharesis.

b. Chelation therapy: Iron overload is in direct proportion of the frequency of blood transfusions and degree of hemolysis. Each 300 ml of packed cells delivers ~200 mg of iron that cannot be excreted by physiological means. Removal of excess iron is as important as transfusion therapy and requires use of iron chelators, starting as early as possible. Three chelating agents are commonly used in India:

- *Subcutaneous Desferrioxamine* (25–50 mg/kg/day) delivered via portable infusion pump over a period of 8–12 hours during night, at least for 5–6 nights/week. Simultaneous administration of oral vitamin C enhances effectivity of chelation. Important toxic effects are growth failure, cataract, hearing impairment as well as increased risk of yersinia infections.
- *Oral Deferiprone* (75 mg/kg/day q8hr) is convenient but not as effective as desferrioxamine and usually used as adjuvant to parenteral chelation. Important toxicity of deferiprone is arthropathy, neutropenia and agranulocytosis.
- *Oral Deferasirox* (20–30 mg/kg/day q24 hr) is the safest chelating agent available at present, though relatively expensive. Common side-effects include gastrointestinal upsets and skin rash. Transient elevation of serum creatinine is common and may require discontinuation of therapy, but progressive renal damage is rare.

  Other oral chelators, including a depot preparation of desferrioxamine that needs to be given only twice a week, are under evaluation.

c. Splenectomy to reduce the rate of hemolysis and RBC destruction is indicated only in cases with—(a) transfusion requirements >240 ml/kg of packed cells in a year, or (b) massive splenomegaly with signs of hypersplenism or risk of traumatic rupture.

However, it should preferably be deferred till 3–5 years, to cross the infection-prone age. Vaccinations against pneumococci, meningococci, *H. influenzae* B, etc., and Penicillin prophylaxis are necessary in splenectomized children.

d. Monitoring for secondary organ dysfunctions: Chronic tissue hypoxia, iron overload, extramedullary erythropoiesis and side-effects of transfusions and chelation therapy, invariably leads to significant secondary organ dysfunctions **(Table 19.12)** in thalassemia major, which must be monitored periodically and managed as required.

TABLE 19.12: Secondary organ dysfunctions in thalassemia

- **Endocrinal dysfunction**
  - Growth retardation (GH deficiency)
  - Delayed puberty and hypogonadism
  - Hypothyroidism
  - T1DM or impaired glucose tolerance
  - Hypoparathyroidism
- **Cardiac dysfunction**
  - Congestive cardiac failure
  - Arrhythmia
- **Hepatic dysfunction**
  - Progressive cirrhosis
  - HBV/HCV infection
- **Skeletal involvement**
  - Osteoporosis
  - Pathological fractures
  - Arthritis
- **Others**
  - Skin bronzing
  - Behavioral issues

e. Bone marrow transplantation (BMT) is best curative option with success rate of ~80–90% if done before significant hemosiderosis develops. Other alternatives for BMT are peripheral stem-cell transplantation and cord blood stem cell transplantation.

f. Other experimental options include:

- ***Gene therapy*** with *in vitro* harvesting of patient's marrow, incorporation of β-globin chains (Zynteglo) in auto-stem cells and reinfusion seems to promising option for ultimate cure in future.
- ***Erythroid maturation agents,*** *e.g.* Luspatercept-a recombinant fusion protein that binds TGF-β family ligands, blocks the signaling pathway involved in ineffective erythropoiesis and improves erythroid maturation.

Stimulants of HbF synthesis, e.g. hydroxyurea (10–20 mg/kg for 4–30 weeks) or other agents, e.g. butyrates, cytosine A, 5-azacytidine, etc. have marginal role in management of thalassemia to neutralize noxious excess of β-chains by increasing α-chain production.

Thalassemia has been recognized as a disability under the right of persons with disability act 2016, which entitles them for various benefits, including reservations in educations and jobs.

Prevention of thalassemia involves = (a) pre-marital testing in high-risk populations, (b) genetic counseling in affected persons, and (c) prenatal diagnosis by mutation analysis in amniotic fluid or chorion villus sampling during subsequent pregnancies. This requires establishing the mutation in the previously affected child and carrier parents and use of FISH technique for prenatal diagnosis.

α-thalassemia is rare and deletion of all four α-globin genes is incompatible with life and presents as hydrops fetalis at birth, since α-chains are part of all hemoglobins beyond embryonic period. However, α-thalassemia with partial deletion presents either as silent *carriers* (deletion of one α-gene), *trait* (deletion of two α-genes) or HbH disease (deletion of three α-genes).

Mixed Hemoglobinopathies: Many other genetic variants of thalassemia often co-exist in some populations with wide clinical spectrum ranging from asymptomatic disease to moderate haemolytic anemia including δβ-*thalassemia* (partial deletion of both δ-and β-genes), *E*β-*thalassemia*, i.e. HbE disease (lysine-glutamic acid at 26) with β-thalassemia mutation, etc.

19.5.4 SICKLE CELL DISEASE

Sickle cell disease (SCD) or Sickle cell anemia (SCA) is the second commonest hemoglobinopathy in India, though more common in African or American blacks.

Epidemiology: In India, SCD is highly prevalent in some aboriginal tribes, e.g. Teli, Mahar, Kunbhi, etc. of central India (Vidarbha, Chhattisgarh, Jharkhand, Odisha). About 4.3% of Indian population is estimated to carry sickle cell gene either in homologous or heterologous state.

Genetic defect: SCD is an autosomal recessive defect of the β-globin gene located on chromosome 11, characterized by *substitution of glutamic acid by valine at the 6th position,* leading to formation of an abnormal hemoglobin (HbS) instead of normal HbA, as follows:

- *Homozygous sickle cell disease (SS)* with complete replacement HbA by HbS, or
- *Heterozygous sickle cell trait (AS)* with HbS concentration of 35–45%

Many cases have *mixed hemoglobinopathies*, i.e. HbS-thalassemia, HbS-C disease.

Pathogenesis: In normal oxygenated state, HbS functions normally. However in hypoxic states, deoxygenated HbS develops abnormal coupling of globin chains to deform the shape of RBCs into a sickle form. While this sickling is reversible in initial stages, persistent hypoxia leads to irreversible sickling of RBCs, which are then trapped in microvasculature *or* spleen to produce vaso-occlusive crises and hemolysis, respectively. Sludging of deformed RBCs in small vessels further aggravates hypoxia and sickling.

Thus, three factors are mainly responsible for pathogenesis of SCA—(a) vaso-occlusive events, (b) chronic hemolysis, and (c) local as well as generalized hypoxia due to *'a'* and *'b'* respectively.

Clinical manifestations of SCA depend on whether the case is homozygous or heterozygous. Presence of high fetal Hb (which does not have β-chains) prevents manifestations of SCD during first few months of life.

Homozygous sickle cell disease usually manifests after 4–6 months of age with:

- ***Chronic hemolytic anemia*** with moderate pallor and signs of chronic hypoxia, e.g. exertional dyspnea and growth failure. Signs of hemodynamic decompensation, e.g. CCF and cardiomegaly may develop in severe cases, while older children may also develop gall stones due to excess bilirubin production.
- ***Moderate splenomegaly*** with/without hypersplenism. Splenomegaly frequently regresses after 5–6 years due to repeated splenic infarcts (autosplenectomy). Altered splenic functions predispose these children for serious infections, e.g. sepsis, meningitis and osteomyelitis by capsular organisms, e.g. pneumococci, *H. influenzae* and Salmonella.
- ***Signs of microvascular ischemia*** and recurrent infarcts, e.g. clubbing, nephropathy, chronic leg ulcers, recurrent epistaxis, etc. *Sickle cell nephropathy* is characterized by recurrent hematuria and hyposthenuria, i.e. loss of concentration capacity due to recurrent medullary infarcts.
- ***Acute crises episodes,*** which may be spontaneous or develop after exposure to hypoxic events, e.g. fever,

infections, dehydration, acidosis and high altitudes. Four main types of crises, seen in SCD are as follows:

- ***Vaso-occlusive crises*** are most common and usually spontaneous with wide clinical spectrum, e.g. sudden painful swelling of hands and feet due to ischemic necrosis of small bones (*Hand-foot syndrome)*, acute abdominal pain (mesenteric ischemia), cerebrovascular strokes, acute chest syndrome (pulmonary embolism), sudden blindness (retinal vein occlusion) and priapism (venous obstruction in corpora cavernosa).
- ***Sequestration crises*** with massive splenomegaly and circulatory collapse due to sudden pooling of blood in the spleen, are more common in younger children, usually after an acute febrile illness.
- ***Hyperhemolytic crises*** with sudden and severe hemolytic episodes are seen in cases with coexisting G6PD deficiency.
- ***Aplastic crises*** with sudden bone-marrow depression and pancytopenia are usually associated with parvovirus B_{19} infections.

Heterozygous sickle cell trait is usually asymptomatic, though mild vaso-occlusive manifestations may develop in severe hypoxic conditions. Identification of these cases by high-risk/family screening is important for genetic counseling.

Mixed hemoglobinopathies usually have milder presentations, except HbS-β thalassemia, which is clinically indistinguishable with SS disease.

Laboratory diagnosis depends on:

- ***Peripheral smear*** showing characteristic *sickled* RBCs with poikilocytosis, target cells, nucleated RBCs and Howell-Jolly bodies (signs of splenic dysfunction).
- ***Sickling test***—a simple screening test to demonstrate sickling in suspected cases.

  Place two drop of freshly prepared 2% sodium hypochlorite solution (reducing agent) over blood smear and seal it with the wax. Examine this slide after 15–20 minutes (for early sickling) and again after 1–2 hours (for late sickling). Early sickling indicates sickle cell disease. Late sicking is also positive in sickle cell trait.
- ***Hb electrophoresis*** is confirmatory and helps to differentiate disease (HbS >80–90%) from carrier state (HbS ~30–40%). It also helps to detect mixed hemoglobinopathies **(Table 19.13)**.

Other investigations may reveal non-specific evidences of hemolytic disease, e.g. moderate anemia, high reticulocyte count, hypercellular marrow with erythroid hyperplasia and mild hyperbilirubinemia.

Prenatal diagnosis is possible at 12 weeks, by DNA-PCR studies on fetal fibroblasts for genetic defect.

Management of these cases include:

- *Prevention and early treatment of precipitating events*, e.g. fever, infections, dehydration, acidosis and hypoxia due to any cause including high altitude.

TABLE 19.13: Hb electrophoresis in sickle cell syndromes

	HbA %	*HbS %*	*HbA_2 %*	*HbF %*	*HbC %*
SS disease	0	85–95	2–3	5–15	–
SA trait	55–60	40–45	2–3	–	–
S-Thalassemia	0–20	60–80	3–5	10–20	–
S-C disease	0	45–50	–	–	45–50

All values in % of total Hb

- *Supportive treatment in acute crises,* with fluids/ electrolyte correction, alkali therapy to prevent acidosis and blood transfusions. Exchange transfusion is indicated in cases with severe life-threatening vaso-occlusive crises, e.g. strokes or acute chest syndrome, to bring down HbS levels <30%. Simple analgesics, e.g. paracetamol and cold fomentations may be used to reduce pain in mild vaso-occlusive crisis.
- *Treatment of chronic anemia*: Repeated transfusions are generally not required, except in severe cases or during crises. However, life-long folic acid supplements are necessary in all cases due to increased erythropoietic activity.
- *Prevention of infections* (due to splenic dysfunction) with pneumococcal, meningococcal and *H. influenza* B vaccines. All cases are also advised oral penicillin prophylaxis from 3 months to 5 years to prevent these infections.
- *Hydroxyurea*-a myelosuppressive agent to stimulate HbF production, is known to reduce hospitalizations due to vaso-occlusive episodes and need for blood transfusions by ~50%. It is relatively safe and well tolerated in children >2 years of age, except potential but reversible risk of bone marrow suppression. Typical starting dose is 15–20 mg/kg/day OD, which may be increased by 5 mg/kg every 8 weeks to a maximum of 35 mg/kg/day. It should be temporarily discontinued if absolute neutrophil count falls <2,000/ mm^3 or platelets fall <80,000/ mm^3.

Newer therapeutic options in selected cases include (a) other HbF stimulating agents, e.g. butyrate and 5-azacytidine, (b) HbS reducing agents, e.g. DDAVP and calcium channel blockers, (c) Membrane stabilizing agents, e.g. zinc, (d) Hb solubility increasing agents, e.g. urea, cynates, etc.

Some other drugs have also been recently approved to prevent SCD crises in older children including, *L-Gutamine* to reduce RBC adhesions to endothelium (PO 5–15 gm BD >5 years); *Voxelotor* to inhibit HbS polymerization (PO 1500 mg/day >12 years); and *Crizanlizumab* to prevent recurrent vaso-occlusive crises in cases >16 years.

Hematopoietic stem cell transplant must be considered in cases refractory to medical treatment.

Prevention: *Genetic counseling*, carrier detection and prenatal diagnosis is essential in all cases to prevent further morbidity in family.

19.5.5 AUTOIMMUNE HEMOLYTIC ANEMIA

Autoimmune hemolytic anemia (AIHA) is characterized by development of antibodies against own RBCs, *either* due to inappropriate immune response to a normal RBC antigen *or* alteration of RBC antigens by some disease/drugs, to render them 'foreign' or antigenic.

Types: Depending on the immunological abnormality, AHA may be classified as:

- *AIHA with warm antibodies* (usually IgG class), which are active between 35–40°C (common in children and usually idiopathic in origin)
- *AIHA with cold antibodies* (usually IgM class), which are most active <37°C (rare in children and usually secondary to some disease)
- *Drug-induced* immune hemolytic anemia.

Etiology: Common causes of AIHA are:

- Primary *or* idiopathic
- Secondary
  - *Infections:* EBV, mycoplasma, other viruses
  - Lymphoproliferative disorders and neoplasms
  - Connective tissue disorders, e.g. SLE
- *Drugs:* Penicillin, quinine, methyldopa

Clinical manifestations may be of two types:

- *Acute transient hemolytic anemia* (70–80%), with sudden hemoglobinuria, rapidly progressive pallor, jaundice and splenomegaly. This presentation is common at 2–12 years of age, characterized by absence of underlying disease in most cases, spontaneous recovery in 3–6 months and good response to steroids.
- *Chronic hemolytic anemia*, persisting for many years is common in infants or adolescents. These cases usually have underlying systemic disease and do not respond well to steroids.

Diagnosis depends on: (a) exclusion of other causes for acquired hemolytic anemia, (b) strongly positive *direct Coomb test* suggestive of the presence of antibodies on RBC surface, and (c) frequently positive *indirect Coomb test* suggestive of the presence of free antibodies in serum.

Management: While no treatment is needed in mild cases, moderate/severe AIHA is treated with:

- Blood transfusions (cross-matching may be difficult in these cases).
- Long-term steroids (PO Prednisolone 1–2 mg/kg/d q6hr for 4–8 weeks or till normalization of hemoglobin, followed by low-dose alternate day maintenance therapy for 3–6 months.
- IV immunoglobulins (1 gm/kg/day x 2 days) and plasmapheresis in steroid non-responsive cases.
- Immunosuppressive therapy with cyclophosphamide, cyclosporine must be considered in steroid-refractory or dependent cases. Rituximab (anti-CD20) monoclonal antibodies have shown a response rate of 80% in AIHA with cold agglutinins, not responding to steroids.

  Splenectomy leads to sustained remission in > 50% cases, though should be avoided in children.

  Other newer therapies include Bortezomib (inhibitor of 26S proteasome) and Eculizumab (monoclonal anti-C5 antibody licensed for paroxysmal nocturnal hemoglobinuria).
- Cases with cold AIHA are unlikely to respond to steroids but usually have a self-limiting course and must be managed with supportive care till recovery, including repeated transfusions.

19.6 APLASTIC ANEMIA

Aplastic anemia (AA) is a sign of bone marrow dysfunction, characterized by pancytopenia *or* bicytopenia due to marked reduction in hematopoietic stem cells *or* progenitor cells of multiple cell-lines. However, isolated pure red cell anemia of bone-marrow origin is not uncommon, which should not be grouped as aplastic anemia (discussed later).

Etiology: Aplastic anemia may be constitutional *or* acquired **(Table 19.14)**.

- ***Constitutional AA*** denotes intrinsic deficiency of stem-cells, seen in many chromosomal/genetic disorders. Commonest cause of constitutional AA is *Fanconi anemia*-usually an autosomal recessive disorders (FANC genes), frequently associated with physical stigmata, e.g. short stature, hyperpigmented skin, multiple café-au-lait spots and bony defects, e.g. hypoplastic thumb.
- ***Acquired AA*** is either due to: (a) destruction of stem cells or colony forming units by direct or immunological marrow injury following infections, drugs, toxins, etc., *or* (b) deficiency of growth factors, e.g. EPO, TPO, etc.. Chloramphenicol was once the commonest drug implicated in acquired AA with estimated risk of ~1/24000–60000 drug administrations.

  Acquired AA is more common than constitutional AA and responds poorly to marrow stimulant therapy.

Clinical presentation: Constitutional AA usually presents at ~5–10 years of age, while acquired AA can

TABLE 19.14: Causes of aplastic anemia

Congenital: (constitutional)
- Fanconi anemia
- Shwachman-Diamond syndrome
- Dyskeratosis congenital

Acquired:
- *Drugs:* Chloramphenicol, cytotoxic agents, NSAIDs
- *Viruses:* Parvovirus B19, EBV, HIV, CMV
- *Toxins:* DDT, benzene, heavy metals
- *Infiltrative lesions:* Leukemia, metastasis
- *Others*: Thymoma, radiation, PNH
- Idiopathic

PNH: Paroxysmal noctural hemoglobinuria

present at any age depending on the cause, with common clinical features of:

- Severe pallor due to erythropenia,
- Bleeding tendencies due to thrombocytopenia,
- Recurrent infections due to leucopenia.

Hepatosplenomegaly is typically absent or minimal. Dysmorphic features, discussed earlier, are common in Fanconi anemia, while features of causative marrow insult may be present in acquired AA.

Diagnosis rests on hematological picture suggestive of depression of all (pancytopenia) or at least two cell lines (bicytopenia), i.e.

- Severe anemia with low reticulocyte count (RPI <1%),
- Leukopenia with absolute neutrophil count <500/mm^3
- Thrombocytopenia (<20,000/mm^3)

Bone marrow examination is essential to confirm the diagnosis (hypocellular bone marrow) and exclude other causes of pancytopenia, e.g. leukemia.

Management: Hematopoietic stem cell transplantation (HSCT) is the only cure for Fanconi anemia and most of other AA, with success rate of 50–80%. Other principles of management include:

- ***Supportive care*** with—(a) avoidance of infections, (b) early diagnosis and treatment of intercurrent illnesses/infections, and (c) repeated packed RBCs/platelet transfusion to maintain safe hematological profile. Prophylactic platelet transfusion is recommended at platelet count <10,000/mm^3 while antibiotic and antifungal prophylaxis is recommended at absolute neutrophil count < 500 cells/mm^3. Routine use of EPO is not recommended, while a short course of G-CSF may be used in cases with serious infections, not responding to antibiotics.
- ***Oral androgen therapy*** has been widely used to treat Fanconi anemia, in whom HSCT is not possible with initial success rate of ~50%, though relapses are common. Oxymetholone or Nandrolone (PO 2–3 mg/kg/day) is commonly used for this purpose, given for 3–4 months followed by gradual tapering. Low-dose steroids may be used concomitantly to minimize growth acceleration and virilising side effects of androgens and prevent thrombocytopenic bleeding by promoting vascular stability.
- ***Immunosuppressive therapy*** is recommended in acquired AA (*not in Fanconi anemia*) with transfusion-dependent or severe disease, if HSCT is not possible. It involves a combination of antithymocyte globulin or ATG (IV 20–40 mg/kg/day × 4–8 days) and cyclosporine (PO 8–15 mg/kg OD), with success rate to induce remission as ~50%. Cyclosporine should be continued for at least 12 months after hematological response, followed by slow tapering to reduce the risk of relapse.
- ***Gene therapy***, though still in evolution phase, has provided fresh hope for these cases.

Prognosis: Spontaneous recovery is rare and long-term prognosis is poor in cases without bone marrow transplant. Even after the transplant, prognosis is guarded due to risk of recurrence and secondary cancers.

Other marrow disorders with isolated or predominant erythropenia are as follows:

Congenital pure red cell aplasia *(Diamond-Blackfan syndrome)* is a rare hereditary (AR/AD) disorder, characterized by an intrinsic defect in *erythroid precursor cells* with relative insensitivity to erythropoietin.

Clinically these cases present with severe anemia by 2–6 months of age. Associated craniofacial and limb defects (triphalangeal thumb) are present in ~1/3rd cases.

Diagnosis depends on combination of-(a) macrocytic or normocytic normochromic anemia with immature RBCs in peripheral smear, (b) low reticulocyte count, (c) reduced erythroid precursor cells in bone marrow, and (d) normal leukocyte and platelet counts.

Treatment with long-term corticosteroids is beneficial, but response is not consistent or persistent. High-dose IV immunoglobulins or methylprednisolone may be used to induce the initial response. Most cases require repeated transfusions with chelation therapy. Bone marrow transplant is rarely helpful.

Outcome: Nearly half of these cases survive till adulthood, with complications, e.g. hypersplenism and hemosiderosis.

Acquired pure red cell anemia is rarer in children than the acquired AA, mostly seen in association with-(a) *viral infections*, e.g. EBV or parvovirus B_{19} infections, (b) *drugs*, e.g. phenytoin, sulfonamides, chloramphenicol, etc., and (c) *thymoma* (due to formation of anti-EPO antibodies).

Most cases respond well to immunosuppressive therapy with steroids or cyclosporin, along with withdrawal of offending drug or treatment of primary cause. Repeated transfusions are necessary till recovery.

Transient erythroblastopenia is relatively more common than congenital or acquired pure red cell anemia, presenting with moderate to severe anemia between 6 months to 3 years. Over 80% cases recover spontaneous in 1–2 months. Exact etiology is not known, but most cases are previously healthy (idiopathic) or have history of minor viral infections.

Anemia in chronic diseases, e.g. infections, inflammatory disorders, malignancies and chronic renal disease is attributed to multiple factors, e.g. (a) bone marrow dysfunction, (b) low erythropoietin levels, (c) nutritional deficiencies and (d) increased hemolysis.

Hematologically, these cases usually have normocytic normochromic/hypochromic anemia with low reticulocyte count and hypocellular bone marrow. Low *serum iron* and *total iron binding capacity* (d/d high TIBC in iron deficiency) is common.

Congenital dyserythropoietic anemia (CDA) are rare inherited normocytic or macrocytic anemias, characterised by multi-nuclearity and abnormal chromatin patterns in RBC precursors suggestive of abnormal bone marrow maturation. Three important variants include:

a. *CDA type I* (15%) presenting any time from infancy onwards with marked erythroid hyperplasia in bone marrow and presence of binuclear erythroblasts (<10% cells), inter-nuclear chromatin bridges between erythroblasts and megaloblasts.
b. *CDA type II* (60%), presenting in second decade with higher percentage of multinuclear erythroblasts (15–30%) and positive HAM test but negative sucrose lysis test (d/d Paroxysmal nocturnal hemoglobinuria).
c. *CDA type III* (15%), is more common in adults with erythroblastic multinuclearity in 10–40% cells (sometimes Gigantoblasts) and negative HAM test.

Clinically, age and severity of presentation may vary from hydrops fetalis at birth to recurrent/persistent hemolytic anemia in older children or adults with mild icterus and hepatosplenomegaly.

Management varies according to severity. While most cases require occasional transfusions, those with frequent transfusion require chelation therapy and may benefit from splenectomy.

Myelodysplastic syndrome is a pre-leukemic stage with 15–20% risk of evolving into acute myeloid leukemia. These cases present at any age with: (a) chronic refractory anemia/pancytopenia, (b) reticulocytopenia despite hypercellular bone marrow, and (c) presence of <5% blast cells in bone marrow.

Diagnosis depends on bone marrow studies and treatment is supportive. Prognosis is poor in cases with secondary transformation into leukemia, though bone marrow transplant may be useful.

19.7 POLYCYTHEMIA

Polycythemia denotes *increase in total red cell mass and Hb levels* above the age-related norms, *excluding* pseudo-polycythemia, i.e. hemoconcentration in dehydration, etc. True polycythemia is characterized by increases in both-the *RBC volume* and the *blood volume*.

WHO defines polycythemia as Hb >16.5 gm/dl (>16 gm/dl in females) or hematocrit >49% (>48% in females) or red cell mass >25% above the mean predicted value, in adults.

In children, *symptomatic* cases with *Hb >16 gm/dl or Hematocrit >45* beyond neonatal period are considered as polycythemic for practical purpose, who need investigations.

Etiology: Polycythemia in children is rarely primary (*polycythemia vera*) and generally indicates excessive erythropoiesis due to persistent hypoxic states or erythropoietin-secreting tumors **(Table 19.15)**.

TABLE 19.15: Causes of polycythemia

- **Secondary (common)**
  - *Neonates:*
    - Delayed clamping of umblical cord
    - Infant of diabetic mother
    - Twin-twin transfusion
  - *Chronic hypoxia:*
    - High altitude
    - Chronic lung disease, cyanotic CHDs
    - *Hb'pathies:* Methemoglobinemia, CO poisoning
  - *Excess erythropoietin (EPO) activity:*
    - Chronic renal disease
    - *EPO secreting tumors:* Hepatic, renal, adrenal
  - *Others:* Cushing syndrome, anabolic steroids
- **Primary (rare)**
  - Polycythemia vera
  - Benign familial polycythemia

CO: Carbon monoxide

Clinical presentation depends on severity and duration of hematological abnormality and include:

- Flushing of skin and mucus membranes,
- Thromboembolic episodes due to blood hyperviscosity,
- Cyanosis and clubbing in severe or chronic cases,
- Iron deficiency due to increased erythropoiesis.
- Features of primary disease.

Management: While severe cases of polycythemia may require periodic phlebotomy, most cases can be managed with exchange transfusion, treatment of primary cause and iron supplementation.

19.8 LEUKOCYTE DISORDERS

Leukocytes are primarily involved in immunological defence mechanisms of body and leukocytic disorders may be *qualitative* or *quantitative*.

Qualitative leukocytic disorders, i.e. functional defects, are *generally inherited* and present with susceptibility to opportunistic infections due to impaired immune functions (Ch 8.2).

Quantitative leukocytic disorders *are* generally *acquired* as a consequence of—(a) immune activity, e.g. infection, inflammation or allergy, or (b) bone-marrow defects, e.g. aplastic anemia or leukemia. These abnormalities may be generalized or limited to one or more components of leukocyte cadre, i.e. *granulocytes* (neutrophils, eosinophils and monocytes) or *lymphocytes*.

Total and differential leukocyte counts (TLC/DLC) vary with age in early childhood, being highest at birth with predominance of polymorphs. While TLC drops gradually to adult level by 7 years, polymorph percentage drops during first 6 months, before rising again to reach adult levels by 4–6 years **(Table 19.2)**.

Some common and important quantitative leukocyte abnormalities are as follows:

Leukemoid reactions: A TLC >50,000/mm^3 is termed as leukemoid reaction, which is usually neutrophilic and

associated with transient appearance of immature cells in circulation, e.g. metamyelocyte and melocytes.

Leukemoid reactions may be seen in—(a) fulminant bacterial infections and septicemia, (b) acute hemorrhage, (c) acute hemolytic reactions, and (d) infections in children with leukocyte adhesion deficiency.

Neutrophils are circulatory phagocytes which mainly act against pyogenic bacteria and are involved in-(a) nonspecific immunity to engulf and digest foreign antigens, and (b) processing of these antigens for further immune reactions. While neutrophils have a short circulatory half-life of ~6–2 hours, large number of partially differentiated cells are present in bone marrow and vascular endothelium (marginating pool), which may be readily mobilized and rapidly differentiated into neutrophils during infections.

Neutropenia is the most important leukocytic abnormality, generally defined as absolute neutrophil counts (ANC) <1500/mm^3 and stratified as *mild* (<1500–1000/mm^3), *moderate* (<1000–500/mm^3) and *severe* (<500/mm^3).

Etiology: Neutropenia may be transient or persistent. *Acute transient neutropenia* usually indicates excessive use of these immunological cells in acute infections, while *persistent neutropenia* may be due to: (a) acquired marrow disorders, e.g. aplastic anemia or leukemia, (b) intrinsic marrow disorders, e.g. cyclic neutropenia, or (c) peripheral destruction in chronic infections or immunological disorders **(Table 19.16)**.

Clinical presentation of neutropenia is directly related to its severity, characterized by increased risk of infections. Mild to moderate neutropenia is generally well tolerated, while localized skin/mucosal infections are more common at ANC <500/mm^3. Very severe neutropenia (ANC <200) is associated with generalized and potentially fatal infections, e.g. septicemia, pneumonia, etc.

Disproportionately less signs of inflammation with minimal pus formation is an important feature of sepsis in neutropenic cases. *Staphylococci* and *gram-negative* bacteria are dominant pathogens in neutropenic children. Neutropenic children are *not excessively prone* to viral, fungal or parasitic infections as well as bacterial meningitis, if not associated with other immunological defects.

TABLE 19.16: Causes of neutropenia

- **Infections:** Viral infections, sepsis, HIV
- **Drugs**
  Immunological: Penicillin, phenytoin, phenobarbitone
  Idiosyncratic: Chloramphenicol
  Cytotoxic: Anti-malignancy drugs, radiation
- **Immune neutropenia**
  Autoimmune neutropenia (Isolated/syndromic*)
  Autoimmune neutropenia of infancy
  Neonatal alloimmune neutropenia
- **Bone marrow defects**
  Inherited: Cyclic neutropenia, Kostmann syndrome
  Acqd: Malignancy, myelodysplasia, aplastic anemia
- **Peripheral sequestration:** Hypersplenism
- **Others:** PEM, megaloblastic anemia

*with other autoimmune disorders, e.g. SLE

Diagnosis rests on serial ANC counts to confirm transient, cyclic or persistent nature of neutropenia, along with bone marrow studies in chronic neutropenia or pancytopenia. Other relevant investigations, e.g. antineutrophil antibodies are indicated in select cases.

Treatment includes early diagnosis and treatment of infections (*see* febrile neutropenia, Ch 10.1.5), along with management of primary cause.

Severe or chronic symptomatic neutropenia may benefit from recombinant G-CSF therapy (SC 3.4–11.5 µg/kg/day), while bone marrow transplant must be considered in severe congenital neutropnia.

Some important causes of neutropenia are as follows:

- **Viral infections** causes of transient neutropenia due to redistribution of neutrophils from circulatory to tissue (marginating) pool. Although neutrophilia is more common in bacterial infections, moderate/severe neutropenia in bacterial infections indicates severe sepsis with poor prognosis.
- **Drug-induced neutropenia** is more common in adults due to several mechanisms, e.g. *toxic* (chemotherapy/radiotherapy), *idiosyncratic* (chloramphenicol) *immunological* (penicillin) or *hypersensitivity* (phenytoin, phenobarb) reactions. While cytotoxic neutropenia is dose-related and appears after 7–10 days of chemo/radiotherapy, others are usually not dose-related.
- **Immune neutropenia** is characterized by *presence of anti-neutrophil antibodies in circulation* with excessive destruction of neutrophils. Important variants include:
  - ***Neonatal alloimmune neutropenia***, like Rh-hemolytic disease, denotes transplacental transfer of maternal alloantibodies (IgG) after prior sensitization. These cases are asymptomatic *or* present with delayed separation of umbilical cord and mild/moderate neonatal infections by *usual* organisms, which respond well to antibiotics. Neutrophil counts normalize by the end of first week. Transient neutropenia is also common in babies born to mothers with autoimmune disorders, lasting longer for few weeks or months.
  - ***Autoimmune neutropenia***, analogous to autoimmune hemolytic anemia or thrombocytopenia, may be an isolated feature or a part of generalized connective tissue disorders.
  - ***Autoimmune neutropenia of infancy*** is a relatively benign disorder that generally presents at 5–15 months of age with recurrent minor or superficial infections in next 6 months-2 years, before

spontaneous recovery. Diagnosis rests on presence of antineutrophil antibodies in serum and treatment includes recombinant human G-CSF therapy, only in cases with severe infection or before surgery.

- **Inherited neutropenia** is rare and indicates intrinsic defects in proliferation and/or maturation of myeloid stem cells, including two important causes:
  - ***Cyclic neutropenia*** is an autosomal dominant defect in proliferation and maturation of myeloid stem cells, characterized by periodic oscillations in ANCs from normal to neutropenia, with an average cycle of 21 days. During neutropenic phase, child may suffer from fever, oral ulcers, sore throat or occasionally, serious infections. Cycles become less prominent with advancing age, reducing severity of symptoms and neutropenia.
  - ***Kostmann syndrome*** (severe congenital neutropenia) is an autosomal recessive disease, characterized by an arrest in myeloid maturation at promyelocytic stage. These cases have severe neutropenia (<200/mm^3) with marked monocytosis and present with recurrent, severe pyogenic infections since infancy. Unless treated with regular G-CSF therapy, most cases die before adolescence due to severe infections.

Neutrophilia, i.e. elevated ANC in peripheral blood, is an indicator of bacterial infection or tissue inflammation, due to-(a) increased mobilization of these cells from bone marrow or marginating pool, as well as (b) actual increase in marrow production.

Normally, up to 5% neutrophils in peripheral blood are in immature forms, i.e. *Band cells*. Presence of >5% neutrophils in band form or as precursor cells, e.g. metamyelocytes, in circulation, indicates rapid turnover of these cells in infections or other stress situations.

Acute neutrophilia is seen in—(a) acute bacterial infection or inflammation, (b) massive tissue injury, e.g. burns, trauma or surgery, (c) chronic hemolytic anemia, (d) drug therapy with adrenaline, steroids and hematopoietic colony stimulating factors. Adrenaline releases neutrophils from marginating pool while steroids accentuate their mobilization from bone marrow.

Chronic neutrophilia is uncommon, seen in—(a) chronic infection/blood loss, (b) vasculitis states, (c) malignancies, e.g. chronic myeloid leukemia, (d) post-splenectomy, and (e) prolonged steroid therapy.

Life-long neutrophilia generally indicate—(a) congenital asplenia, *or* (b) leukocyte adhesion defects; though also seen in Down syndrome or familial myeloproliferative disorders.

Monocytes, i.e. granulocytes with large horse-shoe shaped nucleus, are circulatory precursors of macrophages (tissue phagocytes). After circulatory half-life of 2–5 days, these cells migrate into tissues and transform into macrophages with tissue-specific characters, e.g. Kupffer cells in liver and alveolar macrophages in lungs.

Monocytosis: ***Transient monocytosis*** is common in many bacterial, viral protozoal or rickettsial infections, while ***sustained monocytosis*** is seen in chronic neutropenia, post-splenectomy, and malignant disorders.

Eosinophils are primarily involved in allergic disorders and cytotoxic action against helminths. Through various proteins contained in their granules, e.g. major basic protein, eosinophilic cationic proteins (ECP), eosinophilic peroxidase and eosinophil-derived neurotoxin, etc. Normal eosinophil count varies diurnally, being highest in morning.

Eosinophilia is the hallmark of a*llergic disorders*, though absolute eosinophil count (AEC) does not necessarily correlates with severity of allergy **(Table 19.17)**. AEC is more elevated in acute rather than chronic allergic disorders, sometimes exceeding 20,000/mm^3 (Eosinophilic leukemoid reaction).

Helminthic infestations are another important cause of mild/moderate eosinophilia that parallels with degree of tissue invasion by parasite. Eosinophilia is unlikely in non-invasive parasitic infestations, e.g. giardia or pinworm infestations.

Idiopathic hypereosinophilic syndrome is a leukoproliferative disorder characterized by—(a) persistently elevated AEC >1500 for at least 6 months, (b) absence of other cause, and (c) evidence of systemic organ involvement. Endomyocardial thrombosis and fibrosis are important complication of sustained eosinophilia, though other organs may also be involved. Therapy aims to suppress eosinophilia with corticosteroids. Hydroxyurea may be used in steroid-resistant cases. Most cases with organ involvement or steroid resistance die within 3 years of diagnosis.

Eosinopenia is relatively uncommon, may be seen in some cases with—(a) corticosteroid therapy, and (b) active bacterial/viral infections.

Lymphocytes have a central role in antigen-specific immune response, though also participate in non-antigen specific immunity.

Circulating lymphocytes may be classified according to the morphology (large *vs* small lymphocytes) *or* site of development (T *vs* B cells). T-cells are primarily involved

TABLE 19.17: Causes of eosinophilia

- **Allergic:** Asthma, allergic rhinitis
- **Infections:** Worm infestations, filaria
- **Systemic diseases:**
  - *Lungs:* Tropical pulmonary eosinophilia, Loffler syndrome
  - *GIT:* Chronic inflammatory bowel diseases
  - *Marrow:* T-cell lymphoma, histiocytosis
- **Immunological:** Job syndrome*, Wiskott-Aldrich syndrome
- **Idiopathic** hypereosinophilic syndrome

*Hyper IgE Syndrome

in cellular immunity and further sub-classified according to functions (helper, suppressor *or* natural killer cells) and CD markers (mainly CD_4 *and* CD_8) About 65% of T-lymphocytes carry CD_4 marker with normal CD_4: CD_8 ratio of 1.8:2.0. B lymphocytes are involved in synthesis of immunoglobulins (Ch 8.1).

Lymphocytopenia generally indicates excessive cell destruction in—(a) infections, e.g. HIV, typhoid, (b) drugs, e.g. cytotoxic agents, radiation, steroids, (c) autoimmune disorders, and (d) inherited immunodeficiency disorders, e.g. Wiskott-Aldrich syndrome; though also seen in (e) disorders with ineffective erythropoiesis, e.g. aplastic anemia.

Lymphocytosis is the usual response to—(a) viral infections sp. Infectious mononucleosis, while other important causes include — (b) pertussis, (c) tuberculosis, (d) brucellosis, (e) acute lymphocytic leukemia, and (f) endocrinal disorders, e.g. thyrotoxicosis and Addison disease.

19.9 PHYSIOLOGY OF HEMOSTASIS

Maintenance of intravascular blood in a flowing state is a complex balance between *pro-coagulant activity* to prevent excessive bleeding after trauma and *anticoagulant activity* to arrest disproportionate clotting response and prevent generalized coagulation.

After vascular trauma, hemostasis is achieved by a series of four sequential, interrelated and appropriately limited responses, including—(a) *vascular response*, i.e. reflex vasoconstriction to restrict bleeding, (b) *platelet response* to form a temporary plug at the site of bleeding, (c) *coagulation response* to convert this plug into a stable clot, and (d) *fibrinolytic response* to re-establish vascular potency. Impairment of first three responses leads to *hemorrhagic tendency*, while abnormalities in fibrinolytic mechanisms produce *hypercoagulable states* with thromboembolic complications.

- **Vascular response** is characterized by immediate vasoconstriction at the site of injury to control bleeding, mediated by sympathetic adrenergic activity. Although this response is potentiated further by release of serotonins and other factors from platelets, it rarely lasts for more than few minutes.
- **Platelet response:** Post-injury, exposure of flowing blood to sub-endothelial tissues initiates a sequence of platelet responses, i.e.
  - *Adherence* of platelets to von Willebrand factor (*vWf*)-a protein serving as ligand for platelets at exposed/injury site
  - *Activation* of adhered platelets to release various factors, e.g. *ADP* and *thromboxane* A_2, etc. from their storage granules, which promote further platelet aggregation and activate clotting mechanisms.
  - *Aggregation* of platelets, leading to formation of a temporary *platelet plug* which acts as nidus for clot formation by coagulation mechanisms.
- **Coagulation response** is a complex and sequential activation of various plasma proteins, i.e. clotting factors **(Table 19.18)** and tissue factors, leading to formation of stable clot at the site of injury. Whole clotting cascade may be divided into three phases **(Fig. 19.8)**:

TABLE 19.18: Coagulation factors

I	Fibrinogen
II	Prothrombin
III	Thromboplastin*
IV	Calcium*
V	Proaccelerin (Labile factor)
VI	Accelerin*
VII	Proconvertin (Stable factor)
VIII	Antihemophilic factor
IX	Christmas factor
X	Stuart-Prower factor
XI	Plasma thromboplastin antecedent (PTA)
XII	Hageman factor
XIII	Fibrin-stabilizing factor

*No longer considered as clotting factors (as not independent proteins). Factors' numbers represent order of discovery, not the order of activation.

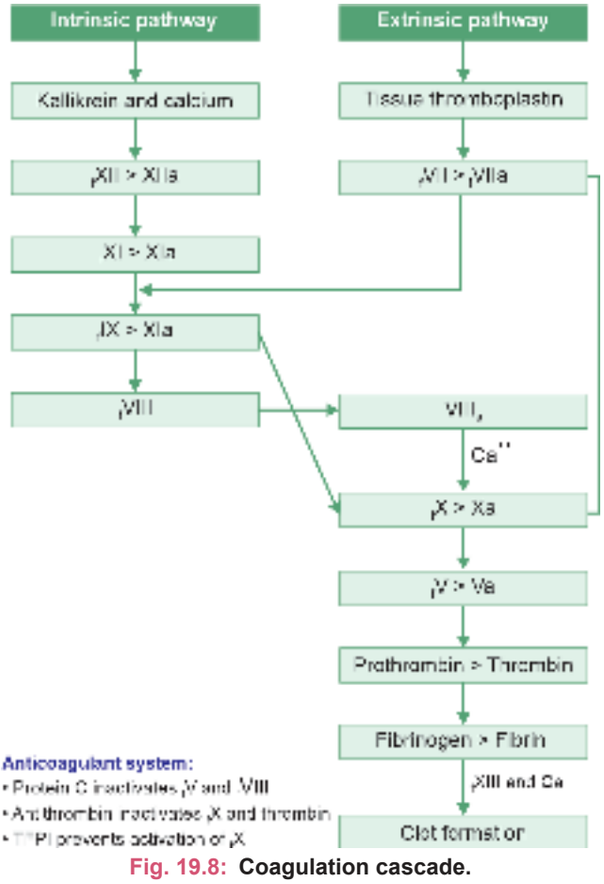

Fig. 19.8: Coagulation cascade.

TFPI: Tissue factor pathway inhibitor

- Activation of $_fX$ by intrinsic *or* extrinsic pathway. ***Intrinsic pathway*** begins with activation of $_fXII$ by two plasma proteins, i.e. *prekallikrein* and *kininogen* that leads to sequential activation of $_fXI$ and $_fIX$. $_fIX$ in presence of $_fVIII$, calcium and phospholipids activates $_fX$. $_fX$ and $_fIX$ activation is also stimulated by an ***Extrinsic pathway*** involving tissue thromboplastin, $_fVII$, and Calcium.
- Activated $_fXa$ activates $_fV$, which along with platelet phospholipid and calcium converts inactive *prothrombin* into active *thrombin* ($_fIIa$).
- Thrombin facilitates conversion of plasma fibrinogen to fibrin, which is further cross-linked by $_fXIII$ to form a stable *fibrin-platelet plug*.

- **Anticoagulant activity:** Excess thrombin generation is limited by many anticoagulants, which include-*inhibitors of thrombin generation*, e.g. protein C, its cofactor protein-S and tissue factor pathway inhibitor (TFPI); and *inhibitors of thrombin activity*, e.g. antithrombin III (AT-III), α_2 macroglobulins (α_2M) and heparin cofactor.

  It is stimulated by binding of thrombin to thrombomodulin on exposed endothelial surface, which activates protein C. Activated protein C inactivates $_fV$ and $_{fV}III$, while AT-III regulates $_fXa$. TFPI-the final inhibitor, stops activation of $_fX$ by $_fVII$ and tissue factor.
- **Fibrinolytic system** aims to lyses the clot to re-establish vascular integrity **(Fig. 19.9)**. Critical enzyme in this process is the *Plasmin*, which forms by activation of plasminogen by tissue plasminogen activator (tPA) and urokinase (UK), and cleaves the fibrin to form fibrin-split products (FSP) including a specific fragment, i.e. D-dimer. Excess plasmin activity is primarily inhibited by $\alpha_2$antiplasmin (α_2AP), while many other proteins inhibit its generation by blocking plasminogen activators-most important in childhood being PAI_1.

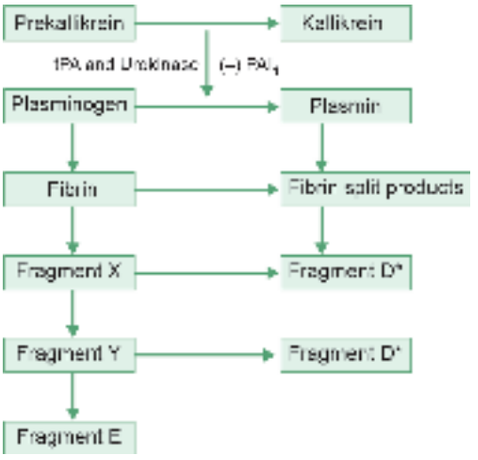

Fig. 19.9: Fibrinolytic system.
*Assayed in D dimer assay
α_2AP: α_2 antiplasmin; **tPA:** Tissue plasminogen activator; **PAI_1:** Plasminogen activation inhibitors

19.10 HEMORRHAGIC DISORDERS

The term *Hemorrhagic disorders* includes a group of heterogeneous congenital or acquired defects, all characterized by *abnormal tendency to bleed*, either spontaneously or after trauma. Though frequently used interchangeably, the term *bleeding disorders* denotes platelet dysfunction, while *coagulation disorders refer to* abnormalities of clotting cascade.

Etiologically hemorrhagic disorders include:

I. Disorders of vascular phase:
- *Physiological: Devil's pinches* in newborns
- *Vasculitis:* Meningococcemia, dengue, SLE, HSP
- *Collagen defects:* Scurvy, Ehlers-Danlos syndrome
- *Miscellaneous:* Hereditary hemorrhagic telangiectasia, Cushing disease, steroids

II. Disorders of platelet phase: (Ch 19.11)
- *Quantitative* defects (Thrombocytopenia)
  - Idiopathic thrombocytopenic purpura
  - Secondary thrombocytopenia
- *Qualitative* Platelet function defects

III. Disorders of coagulation (Ch 19.12)
- *Inherited*, e.g. hemophilia, von Willebrand disease
- *Acquired*, e.g. vitamin K deficiency, chronic liver disease

Diagnostic evaluation for bleeding disorder initially aims to differentiate between—(a) bleeding and clotting disorders **(Table 19.19)**, and (b) inherited and acquired defects. Further investigations are needed to identify precise defect for rational therapy and genetic counseling.

Detailed history must include: (a) age of presentation, (b) site of bleeding (superficial/deep), (c) onset of bleeding (spontaneous/post-traumatic), (d) past history of similar episodes, (e) family history of similar events (specially on maternal side), (f) history of drug intake, e.g. aspirin, NSAIDs, etc.. Menorrhagia may be the only manifestation of disorders like von Willebrand disease or platelet function defects in adolescent females.

Clinical examination should search not only the probable cause (e.g. chronic liver disease), but also for signs of concealed bleeding, e.g. intracranial hemorrhage, which may be life-threatening.

Hess test is a bed-side test to assess capillary fragility, seen in many bleeding disorders. In this, pressure is applied to the forearm with a BP cuff inflated between systolic and diastolic pressure for 10 minute. Appearance

TABLE 19.19: D/D bleeding and clotting disorders

Feature	*Bleeding disorder*	*Clotting disorder*
Commonest cause	ITP	Hemophilia
Age of onset	Post-infancy	Since birth
Site of bleeds	Generalized	Deep and local
Onset of bleeds	Spontaneous	Post-trauma
Duration of bleeds	Self-limiting	Prolonged
Family history	Rare	Common
Past history	Absent	Present
Bleeding time	Prolonged	Normal
Clotting time	Normal	Prolonged
Platelet count	Low/normal	Normal
Clotting profile	Normal	Abnormal

ITP: Immune thrombocytopenic purpura

TABLE 19.20: Interpretation of clotting tests

Platelet count	*PT*	*PTT*	*Possible cause*
Abnormal bleeding time			
↓	N	N	ITP/TCP
N	N	N	Platelet function defects
N/↓	N	↑	vWD disease
Normal bleeding time			
N	N	↑	$_f$VIII, IX, XI, XII deficiency
N	↑	N	$_f$VII deficiency
N	I	↑	HDN, liver disease
			$_f$I, II, X deficiency
N	N	N	$_f$XIII deficiency

TCP: Thrombocytopenic purpura; **VWD:** von Willebrand disease; **HDN:** Hemorrhagic disease of newborn

of >15 petechiae within 5 cm diameter over forearm indicates increased capillary fragility. It is also positive in thrombocytopenia.

Laboratory investigations: While most cases may be identified on the four screening tests—BT, platelet count, PT and PTT **(Table 19.20)**. Other useful investigations include:

- ***Complete blood counts with peripheral smear*** help to identify extent of anemia, involvement of other cell lines (leukemia, aplastic anemia) and platelet count/function.

  Absence of platelet clumps on smear indicates severe thrombocytopenia (<10,000–20,000/mm^3) while inadequate clumping despite normal platelet count indicates possible aggregation defects. Presence of large-size platelets indicates excessive peripheral destruction or *Bernard-Soulier syndrome* (Giant platelet syndrome).
- ***Platelet count*** differentiates between bleeding vs. clotting disorders and between thrombocytopenic purpura vs. platelet function defects.
- ***Ivy bleeding time (BT),*** is measured as time required for hemostasis after a superficial skin incision of 1–2 mm depth and ~5 mm length in forearm, with a BP cuff tied above the incision and pressure maintained at 40 mmHg. *Normal value is 4–8 minutes.* Prolonged BT indicates thrombocytopenia or platelet function defects.
- ***Platelet function tests*** usually include *aggregation studies* after addition of an agonist, e.g. ADP, epinephrine, collagen, thrombin and ristocetin, to activate platelet-rich plasma. These tests aim to identify qualitative defects like Glanzmann's thrombasthenia. *Clot retraction* is defective in both thrombocytopenia and thrombasthenia.
- ***Clotting profile***: Various phases of clotting cascade are assessed as follows:
  - *Lee-White clotting time (CT)* is too unreliable to have a diagnostic value, and may be normal (5–8 minutes) even in severe clotting defects.
  - *Activated partial thromboplastin time (aPTT)* measures intrinsic pathway of clotting cascade, with normal values ranging from 25–40 seconds (compare with control).
  - *PT (Prothrombin time)* measures extrinsic pathway as well as common pathway, following the activation of tissue factor. Normal values are between 10–13 seconds (compare with control, denoted as "Prothrombin index").
  - *Thrombin time (TT)* measures final step of the conversion of fibrinogen to fibrin, with normal value as 11–15 seconds. Prolonged TT indicates afibrinogenemia, hypofibrinogenemia or heparin therapy.
  - *Mixing studies* differentiate between clotting factor deficiencies and presence of factor inhibitors. Correction of abnormal PTT by adding exogenous factor, i.e. normal plasma, indicates a clotting factor deficiency, while persistent abnormality suggests presence of $_f$VIII, $_f$IX or $_f$XI inhibitors.

    Mixing studies are also be used to differentiate between fVIII, $_f$IX and $_f$XII deficiencies. fVIII is present only in plasma but not in serum, while fIX is present in serum but not in plasma. $_f$XI is present in both serum as well as plasma. Correction of abnormal PTT after addition of normal plasma (not by serum) or normal serum (not by plasma) indicates $_f$VIII and $_f$IX deficiency, respectively. $_f$XI deficiency may be corrected by addition of both-normal plasma or serum.
  - *Specific clotting factor assays* are used to establish the presence/severity of specific factor deficiencies.

– *Urea solubility test* is used to detect $_f$XIII deficiency by abnormal solubility of blood-clot in 5M urea solution and short euglobulin lysis time.

19.11 PLATELET DISORDERS

Platelets are non-nucleated blood cells produced in bone marrow as well as other tissues by fragmentation of megakaryocytes, under control of *Thrombopoietin* hormone.

Normal platelet count varies between 1,50,000 and 4,50,000 cells/mm^3. These cells have *in vivo* life span of *7–10 days*, but *in vitro* half-life in only 6–8 hours.

Purpura is a clinical abnormality of platelet-or vascular-phase of hemostasis. Platelet defects may be quantitative (thrombocytopenic purpura) or qualitative (non-thrombocytopenic purpura) **(Table 19.21)**.

19.11.1 IMMUNE THROMBOCYTOPENIC PURPURA

ITP is the commonest platelet disorder in children, characterized by profound *deficiency of circulating platelets* due to excessive peripheral destruction (<1,00,000/mm^3), with normal/increased number of megakaryocytes in bone marrow.

ITP may be broadly divided into:

- *Primary* (>80%), which is usually autoimmune in origin with idiopathic etiology and acute self-limiting course, and
- *Secondary* (~20%), is usually associated with other autoimmune disorders, e.g. SLE, rheumatoid arthritis, etc., with prolonged or recurrent course.

Etiopathogenesis: Primary ITP is characterized by presence of auto-antibodies against the platelet membrane antigens, bonded to platelets.

Major antigenic target in acute ITP is *PlA1 platelet antigen*, i.e. glycoproteins type GPIIb/IIIa of platelet membranes. These antibody-coated platelets are then destroyed in spleen, leading to thrombocytopenia. There is some evidence that these antibodies also act on megakaryocytes to interfere in platelet production.

While exact pathogenesis for platelet-antibody formation is uncertain, acute ITP is more common in children with HLA-B8 and B12 tissue types, suggestive of a genetic predisposition.

However, history of preceding viral infection (~1–4 weeks) in >50% cases also suggests the role of prior sensitization for antibody production.

Clinically, primary ITP is more common in 2–8 years of age group, with equal sex distribution. Clinical signs appear only when platelet count drops below 50,000–70,000/mm^3 with acute onset of:

- *Cutaneous bleeding* as multiple petechial, purpuric or ecchymotic lesions, *in an apparently healthy child.* These lesions are earliest and often only presentation, more prominent on extensor aspects of arms and chest **(Fig. 19.10)**. *Mucus membrane bleeding*, e.g. gum bleeding and epistaxis is present in ~1/3rd cases.
- *Systemic bleeding* like hematuria and GIT bleeding is present in severe cases (<20,000/mm^3), though intracranial bleeding is rare till platelet counts drop <10,000/mm^3.
- Absence of significant hepatosplenomegaly
- *Self-limiting course:* Acute phase lasts for ~2 weeks, when spontaneous bleeds subside though low platelet counts may persist for many weeks. Only 10–20% cases may develop chronic ITP, i.e. persistent thrombocytopenia beyond 6 months.

TABLE 19.21: Causes of platelet disorders

Quantitative defects (thrombocytopenic purpura)

- ***Increased destruction***
  - Immune thrombocytopenic purpura (ITP)
    - Idiopathic (usually acute)
    - Secondary or autoimmune (usually chronic)
    - Neonatal alloimmune thrombocytopenia
  - Mechanical
    - Hypersplenism
    - *Microangiopathic hemolysis:* HUS, TTP, DIC
    - *Others:* Kasabach-Merritt syndrome, drugs
- ***Decreased production***
  - BM infiltration, e.g. leukemia, histiocytosis
  - Aplastic anemia
  - Rare inherited disorders
    - Congenital amegakaryocytic thrombocytopenia
    - TAR syndrome (with absent/deformed radii)
    - Wiskott-Aldrich syndrome

Qualitative defects (platelet function defects)

- ***Inherited***
  - Glanzmann thrombocytopenia
  - Thrombopathic thrombasthenia
  - Gray-platelet syndrome
- **Acquired**
  - Chronic liver/renal disease
  - Drugs, e.g. aspirin, sodium valproate

HUS: Hemolytic uremic syndrome; **TTP:** Thrombotic-thrombocytopenic purpura; **TAR:** Thrombocytopenia with absent Radii

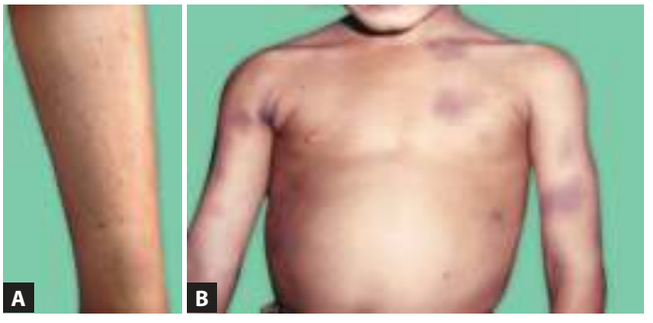

Fig. 19.10: Idiopathic thrombocytopenic purpura: (A) Purpuric spots over legs; (B) Ecchymotic patches over chest and arms.

Diagnosis is largely clinical, based on acute bleeds in an otherwise healthy child without hepatosplenomegaly, supported by:

- Prolonged BT with normal PT/PTT,
- Thrombocytopenia (<1,00,000/mm^3),
- Presence of large platelets on peripheral smear,
- Presence of anti-platelet antibodies in >80% cases,
- Normal bone marrow, except increased number of megakaryocytes due to increased turnover.

Bone marrow exam is not essential for diagnosis, indicated only in cases with chronic ITP, abnormal leukocyte counts, significant anemia, gross splenomegaly and non-responsive cases.

D/D includes other causes of thrombocytopenia or bleeding disorders, e.g. (a) generalized autoimmune disorders, (b) leukemia, (c) aplastic anemia, (d) hypersplenism, and (e) platelet function defects **(Table 19.22)**.

Management: ITP is a *self-limiting* disease and no treatment is indicated in asymptomatic cases without wet bleeds or platelet count >10,000/mm^3. Most guidelines recommend *wait and watch* policy even in cases with platelet count <10,000/mm^3 but no wet bleeds. The aim of treatment is to prevent or treat hemorrhagic complications and *not* merely to restore platelet count. Management of symptomatic cases depends on the severity and includes:

- ***General measures***, e.g. avoidance of physical trauma including intramuscular injections and drugs, e.g. aspirin. Hospitalization is indicated in cases with clinical bleeding or platelet count <10,000/mm^3.
- ***Platelet transfusion*** is indicated only in cases with life-threatening bleeding or undergoing major surgical interventions. There is no evidence that platelet transfusions raise platelet count significantly as transfused platelets, like autologous platelets, are also destroyed by platelet antibodies.
- ***Immunomodulatory therapy*** is indicated in cases with active hemorrhage, platelet count <20,000/mm^3, or undergoing surgical procedures. These modalities include:
  - *IV immunoglobulin (IVIG)* therapy (1 g/kg/day for 1 or 2 days) is the treatment of choice, which prevents destruction of platelets by blocking Fc receptors of platelets and binding the circulating auto-antibodies.
  - *Corticosteroids*, i.e. Prednisolone (PO 1–4 mg/kg/day q6hr) until the platelet count exceed 20,000/mm^3, followed by gradual tapering. IV methyl prednisolone (30 mg/kg/d × 3–7 days) may be used as an alterative to IVIG therapy for rapid restoration of platelet count above safe limits.
  - *Anti-D immunoglobulin* (IV 50–75 µg/kg) is a cost-effective alternative to IVIG, which bind the Rh+ve RBCs to produce a mild hemolysis. These antibody-coated RBCs are then preferentially cleared by spleen than antibody-coated platelets of ITP, reducing the severity of platelet destruction. Hemolysis produced by these antibodies is a therapeutic effect, rarely enough to cause significant anemia. *Note that* Anti-D immunoglobulins are effective only in Rh+ve children.
  - *Other treatment modalities* like plasmapheresis (to remove platelet antibodies) or cytotoxic drugs (to prevent autoantibodies formation) are rarely needed in acute ITP.

TABLE 19.22: D/D bleeding disorders

Platelet count	*Spleen*	*BM*	*Diagnosis*
↓	–	–	ITP, drugs, sepsis
↓	–	+	Aplastic anemia
↓	+	–	Hypersplenism
↓	–	+	Leukemia
N	–	–	Platelet function defects

BM: Bone marrow abnormalities

Prognosis: Most cases of ITP resolve spontaneously in 3 weeks. However, about 20% of them may continue to have thrombocytopenia for 3–12 months (*persistent* ITP) or rarely even longer than 12 months (*chronic* or relapsing ITP).

Persistent ITP, lasting for 3–12 months, does not need specific treatment except close monitoring, aimed to keep platelet count within safe range (and not to normalize the counts) with intermittent steroids.

Chronic ITP is defined as *persistent symptomatic thrombocytopenia for >12 months* or relapse of symptoms after a few months, respectively.

These cases are more likely females and usually present with mild and insidious illness, which should be thoroughly investigated for underlying secondary causes, e.g. collagen disorder, combined variable immunodeficiency, HIV or von Willebrand disease.

For patients with chronic ITP, whose symptoms are not adequately controlled with first-line therapies or who remain dependent of corticosteroids, second-line treatment options include: (a) TPO-receptor agonists, e.g. Eltrombopag (PO 12.6–25 mg OD) or Romiplostim (1–10 µg/kg SC once a week), (b) Other immunosuppressive agents including Rituximab, and (c) splenectomy.

As spleen is the primary site of sensitized platelet destruction, *splenectomy* is indicated for chronic/recurrent ITP, refractory to medical therapy. However, it should be deferred at least till 6 years of age to reduce risk of infections. Splenectomized children are susceptible for infections by capsular organisms and should receive pneumococcal, meningococcal and *H. influenzae* B vaccines apart from penicillin prophylaxis.

TABLE 19.23: D/D idiopathic *vs* secondary ITP

Character	*Idiopathic*	*Secondary*
Course	Acute	Chronic
Age	2–6 years	<1/>10 years
Onset	Sudden	Insidious
Sex distribution	Equal	Females (3:1)
Past history of infection	Common	Rare
Severity	++	+
Co-morbidity	None	+*
Remission	>80%	Uncommon

*signs of autoimmune disease, e.g. hemolytic anemia, arthritis, etc.

IV Rituximab 375 mg/ m^2 weekly for 4 weeks may be used as to delay splenectomy in children though cost is prohibitive.

Some Important clinical differences between idiopathic and secondary ITP are given in **Table 19.23**.

Maternal ITP and Newborn

About 50% newborns of mothers with active ITP manifest with transient thrombocytopenia with/without postnatal bleeding, due to transplacental transfer of maternal platelet antibodies.

Clinical severity depends on the severity of thrombocytopenia in mother though most cases have mild disease and platelet counts recover spontaneously in next 2–4 months.

Prenatal management of these cases is limited to treatment of maternal ITP, according to her clinical status. Considering higher risk of intracranial hemorrhage during vaginal delivery, some workers advocate a single IVIG dose to mother few days before delivery followed by LSCS, though utility of these measures is controversial. Postnatal management with IVIG, steroids or platelet infusion, depends on neonatal platelet counts, till spontaneous recovery.

Other important causes of purpura in childhood include:

Neonatal alloimmune thrombocytopenic purpura (NATP) is a rare but important cause of neonatal purpura, which may be considered as platelet equivalent of Rh-hemolytic disease. It is characterized by antigenic incompatibility between fetal platelets (PLA-1 Ag +ve) and mother (PLA-1 Ag –ve), which stimulates development of maternal antibodies. These antibodies are then transferred transplacentally to destroy fetal platelets.

Clinically, these cases may present as bleeding neonate with moderate/severe thrombocytopenia during first 2–4 weeks of life. Perinatal intracranial hemorrhage is not uncommon.

Diagnosis rests on detection of maternal alloantibodies in newborn, though *prenatal diagnosis* is possible in high-risk fetus (history of NATP in previous sibling) by cord-blood sampling. Unlike newborns of maternal ITP discussed earlier, *maternal platelet count is normal in NATP*.

D/D includes other causes of bleeding neonate specially maternal ITP and intrauterine infections (Ch 12.16.1).

Management of symptomatic cases includes repeated platelet infusions to maintain platelet counts >20,000/ mm^3, till spontaneous recovery by 2–4 weeks.

Prevention includes—(a) genetic counseling for risk of recurrence and severity in next pregnancy (as in Rh-hemolytic disease, and (b) prenatal diagnosis in high-risk cases with fetal platelet count monitoring by repeated cordocentesis after 18 weeks. All mothers with fetal thrombocytopenia (<20,000/ mm^3) should receive weekly IVIG till term, followed by LSCS delivery (preferably) to prevent perinatal intracranial hemorrhage.

Wiskott-Aldrich syndrome, an *X-linked* disorder, is characterized by thrombocytopenia with tiny platelets, eczema and recurrent infections due to a molecular defect in cytoskeletal protein (WAS protein), present in platelets and T-lymphocytes.

Although thrombocytopenia may improve on splenectomy, definitive treatment requires bone marrow transplant. Lymphoreticular malignancies are common (~ 5%) in later life.

Kasabach-Merritt syndrome is a rare disorder characterized by a superficial or visceral giant hemangioma with intra-lesional platelet trapping (thrombocytopenia) and consequent activation of clotting mechanisms leading to localized DIC and hypofibrinogenemia.

Thrombotic thrombocytopenic purpura (TTP) is predominantly a disease of adults, characterized by a pentad of—(i) fever, (ii) thrombocytopenia, (iii) microangiopathic hemolytic anemia, (iv) abnormal renal functions, and (v) shifting neurological signs due to microthrombi in cerebral circulation.

An acquired deficiency of a metalloproteinase enzyme, responsible for cleaving of vWf, appears to important in etiology of TTP.

Diagnosis rests on the triad of-thrombocytopenia, hemolytic RBC morphology and abnormal renal functions, with *normal coagulation studies*.

Treatment is plasmapheresis, with steroids and splenectomy in resistant cases.

Platelet function defects are relatively uncommon, but should always be suspected in bleeding disorders with: (a) normal platelet count, (b) similar family history, (c) abnormal morphology/clumping of platelets on peripheral smear. A *normal bleeding time does not exclude platelet function defects.*

Platelet functions are commonly measured by platelet aggregometry, i.e. automated measurement of platelet clumping after addition of stimulants, e.g. collagen,

thrombin, ristocetin, etc. Some rare but important platelet function defects include:

- **Glanzmann thrombasthenia** is an autosomal recessive defect in platelet aggregation, due to a fibrinogen receptor (GPIIb/IIIa) deficiency in platelets. Platelet count and morphology is *normal* in these cases.
- **Bernard-Soulier syndrome** is also an aggregation defect, characterized by presence of *giant platelets with thrombocytopenia*, due to absence/deficiency of vWf receptors on platelet membrane.
- **Gray platelet syndrome** is characterized by absence of specific storage granules (α-granules) in platelets, causing aggregation and release dysfunction and grayish appearance of platelets on Wright staining.

19.12 COAGULATION DISORDERS

Coagulation defects (clotting factor deficiencies) may be inherited *or* acquired **(Table 19.24)**, mainly including Hemophilia A and B-both being X-linked recessive, almost always seen in males only. Hemophilia C ($_f$XI deficiency), parahemophilia ($_f$V deficiency) and other coagulation defects are usually autosomal recessive and produce minor hemorrhagic disease.

19.12.1 HEMOPHILIA

Hemophilia is an X-linked recessive deficiency of either $_f$VIII *(classic hemophilia or Hemophilia A)* or $_f$IX *(hemophilia B or Christmas disease)*-the former being more common (80–85%). Hemophilia A occurs in ~1/5000 live male births.

Both defects share common mode of inheritance as well as clinical presentation, but with differences in diagnosis and management.

Etiopathogenesis: $_f$VIII and $_f$IX are essential components of intrinsic clotting pathway, involved in activation of $_f$X and absence of either of these proteins impairs the ability to generate thrombin and fibrin leading to delayed and friable clot formation.

Severity of these disorders depends on the percentage of normal factor activity, graded as: (a) *mild haemophilia* (>5%), (b) *moderate hemophilia* (1–5%), and (c) *Severe hemophilia* (<1%). One unit of each factor denotes the activity of the corresponding factor in 1 ml of normal plasma. Deficiency of von Willebrand factor can also lead to secondary deficiency of $_f$VIII.

Clinical features: Being X-linked diseases, only males are affected, while females are carriers. While some cases may present at neonatal period with bleeding from umbilical stump or during circumcision (as $_f$VII and $_f$IX do not cross placenta), most cases manifest in infancy with:

- *Recurrent spontaneous hemarthrosis* (or after trivial trauma), usually at ankles, knees or elbow with pain and swelling is the commonest manifestation, leading to chronic deformities in older children **(Fig. 19.11)**.
- *Mucocutaneous bleeding*, e.g. easy bruising, excessive and prolonged bleeding after trivial trauma, gum bleeds, intramuscular hematoma, etc.
- *Life-threatening bleeding* in severe disease from GIT, upper airways and intracranial space.
- *Mild hemophilia* may not develop spontaneous hemorrhages but bleed longer following trauma or surgeries and remain undiagnosed for many years.

Female carriers are usually asymptomatic, except those who either have reduced factor levels due to lyonization of X-chromosome *or* have only one sex chromosome, e.g. Turner syndrome (XO).

Laboratory diagnosis is based on:

- *Clotting time (CT)* is prolonged in severe hemophilia, though normal CT does not exclude mild disease.
- *Activated partial thromboplastin time* (aPTT) is the most reliable screening test, which is usually three times higher than in control but can be corrected by mixing with normal plasma.
- *Prothrombin time*, an indicator of extrinsic pathway abnormality, is normal in hemophilia as also the BT, TT and platelet count.
- *Specific factor assays*, though not essential, are useful for diagnostic confirmation and quantification of $_f$VIII and $_f$IX activity.

TABLE 19.24: D/D of coagulation disorders

Inherited clotting factor deficiencies
- Hemophilia A (fVIII)
- Hemophilia B (fIX)
- Hemophilia C (fXI)
- Parahemophilia (fV)
- von Willebrand disease
- *Others:* (fVII, X, prothrombin, XIII, fibrinogen)

Acquired (vitamin K dependent) factors* deficiencies
- Hemorrhagic disease of newborn
- Chronic liver disease/malabsorption
- Prolonged antibiotic therapy
- Disseminated intravascular coagulation (DIC)
- Anti-coagulant therapy

*$_f$II, VII, IX, X

Fig. 19.11: Hemophilia: (A) Mucosal bleeding; (B) Hemoarthrosis.

$_f$VIII has two components — antigenic component ($_f$VIII-Ag) and coagulant component ($_f$VIII-C). In hemophilic cases or carriers, $_f$VIII-C is reduced but $_f$VIII-Ag is normal (*d/d* von Willibrand disease, in which fVIII-Ag activity is reduced).

- *Ancillary investigations*, e.g. joint X-rays and neuroimaging for intracranial bleeds may be required in cases with chronic arthropathy or CNS signs.

Antenatal diagnosis of hemophilia is possible at ~18–20 weeks by assessment of $_f$VIII/$_f$IX activity in cord blood sample. However, many cases could be identified earlier at 14–16 weeks by molecular studies in amniotic fluid; or even at 8–10 weeks by chorionic villous sampling.

Carrier detection in Hemophilia A is based on $_f$VIII-C and $_f$VIII-Ag ratio. A ratio of <0.6 indicates carrier state in females. Molecular diagnosis can also be used identify genetic mutation in carriers.

Management: Comprehensive management of hemophilia is a team-work involving physician, nurse, orthopedic surgeon, physiotherapist and psychosocial workers, which *aims* to control acute bleeding episodes and minimize long-term joint disabilities to improve the quality of life. Important steps in management include:

I. Control of acute hemorrhagic episodes revolves around the factor replacement therapy though local pressure/packing and anti-fibrinolytic therapy (discussed below) may be helpful in minor bleeds.

- **Factor replacement therapy** aims to increase corresponding factor levels above the hemostatic level, i.e. 35–40% (for $_f$VIII) or 25–30% (for $_f$IX), in mild/moderate bleeds and up to 100% in life-threatening intracranial bleeding. However, the options for factor replacement differ in $_f$VIII and $_f$IX deficiency.
  - ***$_f$VIII deficiency*** is best corrected by *purified $_f$VIII concentrates*, which may be plasma-derived or recombinant. Recombinant products are preferred due to less risk of transfusion-related infections. Each bag of $_f$VIII concentrate contains ~200 units and the desired dose is calculated as follows:

    $_f$VIII (Units) = (desired $_f$VIII%) × Body weight (kg) × 0.5

    For example, to achieve plasma level of 40% in a 15-kg child, calculated dose is 40 15 0.5 = 300 units. Each unit of $_f$VIII/kg increases the level by 2% with half-life of 8–12 hours.

    Cryoprecipitate may also be used for $_f$VIII replacement, if concentrates are not available. Each bag of cryoprecipitate contains ~100 units of $_f$VIII but carries the potential risk of volume overload, transfusion-related infections or allergic reactions due to presence of human protein.
  - ***$_f$IX deficiency*** may be corrected by purified $_f$IX concentrates (calculated as above), prothrombin complex concentrates or fresh frozen plasma. Cryoprecipitate is of no use due to little $_f$IX activity.

Considering short half-life of $_f$VII and $_f$IX, these factors need to be transfused every 8–12 hours to sustain desired levels,. However in hemarthrosis and closed-space muscle bleeds, bleeding usually stops with one or two transfusions and does not recur due to surrounding pressure. Treatment of various types of bleeds in hemophilia is shown in **Table 19.25**.

Development of $_f$VIII or $_f$IX antibodies (inhibitors) should be suspected in cases, which do not respond to adequate factor replacement. These antibodies usually develop after repeated transfusions and estimated by quantitative assays (in *Bethesda units*).

TABLE 19.25: Factor replacement therapy for bleeding episodes in hemophilia

Type of bleeding	***Hemophilia A ($_f$VIII replacement)***	***Hemophilia B ($_f$IX replacement)****	***Remarks***
Pressure bleeds			
Hemoarthrosis Muscle hematoma	50 IU/kg on Day 1 > 20 IU/kg Alt day till recovery[1]	60 IU/kg on Day 1 > 30 IU/kg Alt day till recovery[1]	Rest, Aspiration, if required
Superficial bleeds			
Epistaxis, gum bleeds Dental extraction	20 IU/kg, repeat 8-hrly if required	30 U/kg, repeat 12-hrly if required	Pressure pack, Anti-fibrinolytic therapy
Moderate bleeding			
GIT, hematuria	20 IU/kg, repeat 8-hrly if required	30 IU/kg, repeat 12-hrly if required	Fluid/electrolyte correction, Blood transfusion
Severe bleeding			
Intracranial bleeding Major surgery	50-75IU/kg stat > 25 IU q8–12h × 5–7 days > 50 IU/kg q24h × 7days	80 IU/kg stat > 40 IU/kg q 12–24h × 7–14 days	Same as above
Deep tissue bleeds			
Retroperitoneal/ Retropharyngeal bleed Iliopsoas hemorrhage	50 IU/kg stat > 25 IU/kg q12h till symptomatic > 20 IU/kg Alt day × 10–14 day[2]	80 IU/kg stat > 40 IU/kg q12h till symptoms → > 20 IU/kg Alt day × 10–14 day[2]	Same as above

[1]Till recovery or return to baseline joint functions, [2]Total duration of therapy
*$_f$IX doses for plasma-derived products, 30% higher for recombinant products

These patients may respond to higher doses of $_f$VIII or$_f$ IX or need to be treated with activated prothrombin complex concentrates or aPCC ($_f$VIII inhibitor bypassing activity or FEIBA) or recombinant $_f$VIIa (Novoseven).

A new therapeutic option for hemophilia A with/without inhibitors includes *Emicizumab*, a monoclonal antibody, which performs the function of $_f$VIII by bridging $_f$IXa and $_f$X, mimicking activated $_f$VIIIa.

- **Supporting measures** to control active bleeding in hemophilia include:
  - ***Non-factor substitutes:*** *Desmopressin acetate (DDAVP)* releases endogenous $_f$VIII and may be used during elective dental/minor surgical procedures in cases of mild/moderate hemophilia A or von Willebrand disease, but not in severe hemophilia A or B. It is given as 0.3 µg/kg IV in 25–50 ml normal saline over 20–30 minutes *or* as nasal spray. A fibrin glue has been used to seal bleeding sites in minor procedures, e.g. dental extraction.
  - ***Anti-fibrinolytic therapy*** is used to control mucosal bleeds or for dental extraction, using *Tranexemic acid* (PO 25 mg/kg 6-hrly) or *Epsilon aminocaproic acid or EACA* (PO 100–200 mg/kg initially followed by 50–100 mg/kg 6-hrly)
  - ***Local measures,*** e.g. pressure packing/bandage or cold compresses, etc. may be helpful in cases with superficial mucosal/skin bleeds.

II. General care in these cases include:

- *Prevention of bleeding* by avoidance of physical trauma, e.g. contact-sports, IM injections, etc., drugs, e.g. aspirin and good dental care.
- *Correction of anemia*, if necessary, by blood/ packed cell transfusions.
- *Prevention of transfusion related infections* by proper screening of blood products, HBV vaccination, and periodical HIV/HBV screening.
- *Symptomatic therapy* with bed-rest, joint immobilization, cold-compresses and codeine during acute hemarthroses. Analgesics, e.g. aspirin, may inhibit platelet functions and should be avoided. Joint aspirations should be avoided except in severe persistent effusions, and should be preceded by pre-aspirate factor infusion.
- *Prevention of joint deformities* by physiotherapy between attacks and surgical corrections.
- *Social and psychological* support.
- *Rehabilitation* and occupational therapy.
- *$_f$VIII prophylaxis* (15–20 IU/kg thrice a week) is also used in severe haemophilia to prevent deformities, frequent needs of hospitalizations and improve the quality of life.

III. Genetic counseling with carrier detection and prenatal diagnosis, using molecular studies on chorionic villus biopsy sample or amniocentesis.

Long-term complications of hemophilia include: (a) chronic arthropathy, deformities and disabilities, (b) transfusion-related complications and infections, (c) psychological disorders, and (d) development of $_f$VIII or $_f$IX antibodies.

Other important but milder coagulation disorders include:

von Willebrand disease (vWD) is the commonest hereditary bleeding disorder, accounting for ~3–5% of all coagulation defects.

Etiology: vWD is an autosomal dominant disorder involving chromosome 12, characterized by deficiency of von Willebrand factor (vWf) — a carrier protein for $_f$VIII, which also has a role in platelet aggregation.

Consequently, these cases are characterized by combination of two hemostatic defects—(a) $_f$VIII deficiency and (b) platelet aggregation defect. Severity-wise, it is classified as Type I (vWf reduced), Type II (vWf function defect) and Type III (vWf absent).

Clinically most cases present with mild to moderate mucocutaneous bleeding beyond neonatal period. Some cases present only as menorrhagia in adolescents. However, type III may present with severe bleeding in newborns or spontaneous hemoarthrosis in later life.

Diagnosis is supported by a combination of prolonged *bleeding time* (platelet defect) and *PTT* (clotting factor defect), confirmed by quantitative vWf assay. Unlike Hemophilia A, $_f$VIII-Ag activity on Ristocetin assay is reduced in vWD.

Treatment: Mild cases may be treated with antifibrinolytic agents, e.g. EACA or non-factor substitutes, e.g. DDAVP, while severe cases need factor replacement with intermediate-purity $_f$VIII concentrates (which also contain vWf) or cryoprecipitate.

Hemophilia C (factor XI deficiency) is an autosomal recessive disorder with *mild to moderate bleeding* tendency. Replacement therapy is usually required only during surgical procedures, using fresh frozen plasma, as this factor is not available in cryoprecipitate or purified concentrate form.

19.13 DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation (DIC), also termed as *consumption coagulopathy*, is a common and potentially life-threatening problem, characterized by disproportionately excessive activation of coagulant mechanisms, which leads to:

- Generalized microvascular thrombosis (tissue ischemia/necrosis),
- Consumption of coagulation factors (bleeding tendencies) and
- Excessive fibrinolysis (elevated levels of fibrin degradation products).

Etiopathogenesis: DIC is usually a terminal event in many serious illnesses, e.g. infection and hypoxia **(Table 19.26)**.

While clinical presentations are primarily hemorrhagic, disseminated tissue injury is predominantly caused by extensive fibrin deposition in microvasculature and consequent tissue ischemia **(Fig. 19.12)**. Intravascular sludging of RBCs leads to microangiopathic haemolytic anemia. Destruction of excessive formed fibrin in thrombotic process is responsible for increase in fibrin degradation products (FDPs) in these cases.

Clinical features: Most cases are seriously sick with primary disease, when they develop sudden bleeding from venipuncture sites and generalized petechiae, ecchymosis and gangrenous infarctions of skin and subcutaneous tissues.

Rapidly, these cases progress to develop systemic bleeding diathesis with GIT, urinary and pulmonary hemorrhage as terminal events. Features of precipitating event are almost always present.

Investigations: Diagnosis is largely clinical, supported by—(a) thrombocytopenia, (b) abnormal clotting tests (PT, aPTT, TT), (c) microangiopathic haemolytic anemia on peripheral smear (*fragmented, burr and helmet-shaped erythrocytes)* and (d) presence of *fibrin degradation products* (FDPs); last being a common screening test. *D-dimer assay* (a FDP itself) is equally sensitive but more specific than FDP levels.

TABLE 19.26: Causes of DIC

- *Infections:* Gm –ve sepsis, meningococcemia*
- *Post-hemorrhagic:* Head injury, crush injuries
- *Metabolic:* Hypoxia, shock, hypo-/hyperthermia
- *Poisonings:* Snake/insect bites
- *Microangiopathy:* Hemolytic-uremic syndrome
- *Malignancies:* Promyelocytic leukemia, others
- Acute hepatic failure and Reye syndrome
- *Miscellaneous:* Mismatched transfusions

*Purpura fulminans

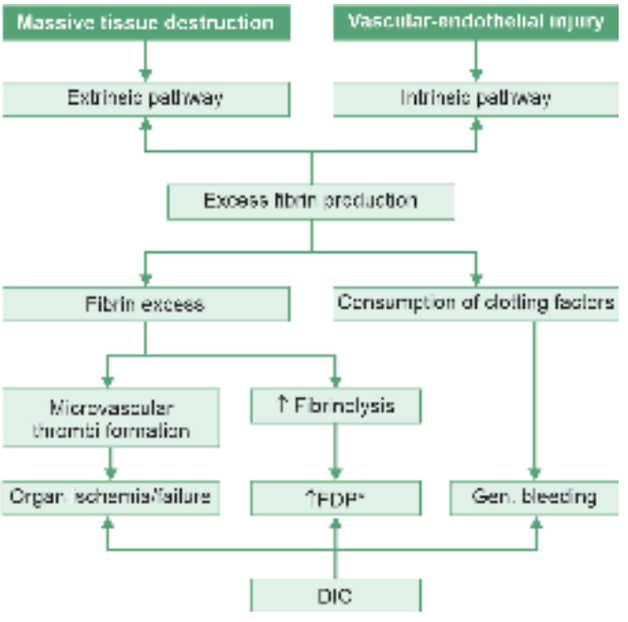

Fig. 19.12: Pathogenesis of DIC.

*fibrin degradation products

Management of DIC includes:

- Treatment of primary cause, e.g. sepsis, acidosis, hypoxia, etc.
- *Pro-coagulant therapy* with 12–24 hourly infusions of FFP (10–15 ml/kg) and platelet concentrates (½–1 bag), to maintain platelet counts >50,000/mm^3 and fibrinogen levels >75 mg/dl.
- *Anti-coagulant therapy* with heparin is indicated in selected cases (slow infusion of 5–10 U/kg/hr) to maintain aPTT at ~1.5–2.0 times of normal.

Despite clinical improvement in bleeding/thromboembolic manifestation and correction of laboratory parameters, heparin does not alter the course of DIC due to underlying disease process. Heparin therapy *should not be used* in septic shock, snake-venom poisoning, heat stroke, head injury and transfusion reactions, unless vascular thrombosis is certain. Antithrombin-III concentrates may be used with heparin in selected cases.

19.14 HYPERCOAGULABLE STATES

Hypercoagulable states or *thrombotic disorders* indicate—(a) deficiency of anti-coagulant factors, (b) excess of pro-coagulants, or (c) relative stasis of blood flow due to any cause, e.g. polycythemia.

Etiologically, hypercoagulable states may be hereditary or acquired **(Table 19.27)**. Acquired disorders, e.g. presence of a vascular catheter, is the commonest cause of thromboembolic episodes in childhood.

Clinical spectrum of thromboembolic complications depends on the severity of defect and primary etiology, ranging from acute *purpura fulminans* to localized and/or recurrent thromboembolic episodes, e.g. deep vein thrombosis, cerebrovascular strokes, pulmonary embolism, renal thrombosis, etc.

Diagnosis of thrombotic episodes depends on the suspected site. While Doppler studies are commonly

TABLE 19.27: Hypercoagulable states in children

- **Inherited procoagulant defects**
  - Protein C/S, plasminogen or AT-III deficiency
  - Protein C resistance (Mutant $_f$V Leiden)
- **Acquired defects (more common)**
  - Sepsis and DIC
  - Cyanotic CHDs
  - Nephrotic syndrome
  - Malignancy
  - Vasculitis syndromes, e.g. SLE, homocysteinuria
  - Prolonged vascular catheterization/immobilization

used for diagnosis of peripheral thromboembolic episodes, venographic studies may be required for doubtful cases of organ thrombosis.

Management of thromboembolic episodes includes treatment of primary cause and removal of thrombus *either* by thrombolytic therapy (Urokinase, Streptokinase, recombinant Plasminogen activator) *or* thrombectomy, along with low molecular weight heparin or LMWH (SC 1–1.5 mg/kg BD) during acute phase to prevent the spread of thrombus. LMWH should be avoided in kidney dysfunction.

Recurrent episodes may necessitate use of prophylactic anticoagulant therapy to maintain an INR between 2 to 3, starting with low molecular weight heparin (SC 0.5–0.75 mg/kg/dose OD), followed by oral warfarin or direct-acting anticoagulants till the risk persists.

Purpura fulminans is a life-threatening condition, characterized by acute hemorrhagic infarction/necrosis of skin due to severe protein C and/or S deficiency.

Etiologically, It may be seen in newborns (hereditary homozygous deficiency) or as an acquired defect in severe sepsis (*Staph. aureus*, Pseudomonas), menigococcemia or viral infections, e.g. chicken pox.

Clinical and hematological picture in these cases resembles DIC with predominant skin involvement.

Treatment is largely supportive, including elimination of primary infection along with heparin or steroids in selected cases.

19.15 SPECIFIC THERAPEUTIC MODALITIES IN HEMATOLOGY

This chapter deals with some unique therapeutic modalities in management of hematological disorders.

19.15.1 BLOOD-PRODUCT TRANSFUSIONS

While blood product transfusions are life-saving, these infusions are not without risks and should be used judiciously with clear indications. It is preferable to use specifically desired blood components, rather than the whole blood in most cases.

Blood products: Whole blood is made up of plasma and cellular components, which can be separated by various centrifugation techniques. These separated blood products are further modified to meet appropriate storage requirements (e.g. frozen plasma) or reduce the risk of adverse reactions (salt-poor albumin, irradiated/saline washed cells). In this way, single donor may be used repeatedly for various components. Some commonly used blood products in children are as follow:

- **Whole blood transfusion** (15–20 ml/kg) should be strictly restricted to cases of—(a) massive blood loss during trauma or surgery, (b) severe anemia *with* shock, and (c) exchange transfusions.

TABLE 19.28: Indications for RBC transfusion[1]

	Hemoglobin
Infants < 4 months	
• Severe CP disease/NICU care	<12 gm/dl
• Major surgery	<10 gm/dl
• Stable anemia	<7 gm/dl
Children > 4 months	
• Severe CP disease/ICU care	<12 gm/dl
• Acute blood loss >10%	—
• Thalassemia/sickle cell crisis*	<10 gm/dl
• Aplastic anemia/marrow failure	<7 gm/dl
• Stable anemia/major surgery	<7 gm/dl

*Preferably exchange transfusion. **CP :** Cardiopulmonary

Each bag of whole blood generally has a volume of 350 ml blood (with 49 ml anticoagulant), Hb content 12 gm/dl and shelf-life of ~35 days. Smaller bags of ~100–150 ml whole blood are also available for pediatric use.

Administration of a diuretic, e.g. furosemide (IV 2 mg/kg) during or immediately after whole blood transfusion, is preferred to avoid fluid overload. Cold blood, supplied by blood bank, should not be infused till it has reached the room temperature.

- **Packed cells transfusions** (10 ml/kg) with fresh or frozen and stored RBCs are preferred in—(a) severe anemia *without* shock, (b) transfusion therapy in thalassemia, and (c) preoperative correction of anemia **(Table 19.28)**.

Each bag of Packed RBCs has a volume of 200 ml, Hb levels of 20 gm/dl and shelf-life of 35 days. All complications and precautions of whole blood transfusions apply for packed cell infusions as well, except lesser risk of fluid overload. Pyrogenic reactions may be reduced by using saline-washed RBCs.

- **Platelet transfusions** (5–10 ml/kg) are generally indicated in—(a) thrombocytopenia with internal bleeding, (b) asymptomatic thrombocytopenia of < 10000/mm^3, or (c) when a surgical intervention is necessary in thrombocytopenic child. However, the critical level at which platelets need to be transfused depends more on the presence or expected risk of severe bleeding rather than absolute platelet counts **(Table 19.29)**.

Each unit of platelets has a volume of ~ 50–70 ml and shelf-life of 3–5 days. These products are very prone for bacterial contamination and should be infused immediately, preferably within 30 minutes, after procurement. Do not store them in refrigerators (2–6°C) as it makes them non-functional.

- **Fresh or fresh frozen plasma,** i.e. FFP (10–15 ml/kg) contain substantial amount of coagulation factors, albumin and globulins; and mainly used in severe multiple clotting factor deficiencies with active bleeding or before invasive procedures, e.g. liver

TABLE 19.29: Indications for platelet transfusions[1]

	Platelet count
Children < 4 months	
• Active bleeding/ Invasive procedures	<50 × 10⁹/L
• Marrow failure with risk factors*	<20 × 10⁹/L
• Marrow failure without risk factors	<10 × 10⁹/L
Infants < 4 months	
• Active bleeding	<100 × 10⁹/L
• Invasive procedure/clinically unstable	<50 × 10⁹/L
• Clinically stable	<20 × 10⁹/L

*e.g. Severe mucositis, **DIC:** Anticoagulant therapy, etc.

TABLE 19.30: Indications for plasma transfusions[1]

- Multiple clotting factor deficiencies with bleeding in -
  - Massive transfusions (Dilutional coagulopathy)
  - Severe liver disease, sp. with S. fibrinogen <1 gm/l
  - Invasive procedures, e.g. liver biopsy with INR > 1.4
  - DIC with INR >1.5
- Single-factor coagulopathies, if specific factor is not available
- Emergency reversal of warfarin effects
- Anticoagulant protein replacement

TABLE 19.31: Complications of blood product transfusions

- **Immediate complications**
  - ***Febrile non-hemolytic transfusion reactions***
  - ***Hemolytic reactions***
    - Mismatched transfusions
    - Accidental infusion of hemolysed blood
  - ***Allergic***
    - Urticaria, anaphylaxis
    - Transfusion-related acute lung injury (TRALI)
  - ***Fluid overload***
    - Transfusion associated circulatory overload (TACO)
  - ***Metabolic disturbances***
    - Metabolic acidosis (with citrated blood)
    - Hyperkalemia (in vitro hemolysis)
    - Hyperphosphatemia (with CPD blood)
    - Hypocalcemia
    - Hyper/hypoglycemia
- **Late complications**
  - ***Infections***
    - *Viral:* HBV, HCV, HIV, CMV
    - *Others:* Malaria, syphilis
  - ***Iron overload:*** Hemosiderosis
  - ***Immunological:***
    - Graft vs. Host disease
    - Late isoimmunization

disease, massive transfusions, DIC or anticoagulant overdose **(Table 19.30)**.

Each plasma bag has a volume of ~150 ml and shelf life is up to 1 year at-30°C. It should be used within 6 hours of thawing a room temperature.

Cryoprecipitate, prepared from the precipitate formed by controlled thawing of FFP, is more concentrated with a volume of 15–20 ml and shelf-life of up to 1 year at-30°C. It is mainly used as an alternative to $_{f}$VIII concentrates or as a source of fibrinogen in DIC

- **Granulocyte infusion** (1–5 × 10^{10} neutrophils/kg), though used sparingly due to high-risk of transfusion reactions, are excellent adjuvant to antibiotic therapy for infections in granulocytopenic cases. However, the methodology to collect and produce proper granulocyte infusates is complex and not easily available at most blood banks.

Other commonly used blood products include immunoglobulins (Ch 9.9), etc. are discussed elsewhere.

Adverse reactions to transfusion of blood products may develop due to errors at: (a) blood-bank levels, e.g. accidental supply of mismatched blood, under-screened blood, old blood, etc. or (b) transfusion level, e.g. accidental freezing/overheating of blood, delayed transfusions, rapid rate of infusion, etc. While various complications of blood-product transfusions are listed in **Table 19.31**, some important transfusion reactions and their management are as follows:

- **Non-hemolytic transfusion reactions** are commonest transfusion reactions due to presence of preformed pyrogens, e.g. leukocytes or bacteria (rare) in blood products. *Clinically*, these reactions present with fever with chills and rigors during or shortly after transfusion, last only for few hours and can easily be controlled by discontinuation of transfusion and symptomatic therapy with antipyretics and/or antihistaminics. Use of saline-washed packed cells helps to prevent these reactions.
- **Allergic reactions** may develop *during or after many hours of transfusions* and present with wide clinical spectrum, ranging from mild urticaria to severe anaphylaxis. Treatment varies according to the severity, though most of them are mild and can be easily managed with simple antihistaminics. Incidence of allergic reactions can be minimized with the use of irradiated blood products. Late immunological reactions, e.g. Graft *vs* Host disease, are discussed later.

Transfusion-related acute lung injury (TRALI) is a rare but serious complication of transfusions, characterized by development of acute respiratory distress during or within 6 hours of transfusions. Although exact pathology is unclear, TRALI is presumed to be precipitated by the infusion of donor antibodies directed against recipient leukocytes, leading to immune-mediated endothelial damage and capillary leak. Most cases require ventilator support before spontaneous recovery within 3–5 days, with high mortality rate of 5–10%.

- **Mismatched transfusion reactions,** although uncommon, may be life-threatening and involve many medicolegal issues.

Clinically, these cases may present with acute hemolysis, hemoglobinuria, shock-like state and progressive renal failure.

Management includes: (a) immediate discontinuation of transfusion, (b) reporting back to blood bank for re-check the cross matching, (c) collection of blood samples for direct Coomb's test, blood counts, clotting profile, liver and renal function tests as well as serial urine examination for hemoglobinuria, (d) intensive clinical monitoring, and (e) supportive therapy with fluid/electrolyte correction and cardioventilatory support.

Re-transfusion with properly matched blood may be necessary for primary indication. Many cases, transfused with mismatched blood for Rh factor (Rh+ve donor to Rh–ve recipient) or minor blood group incompatibility, may not manifest immediately with hemolysis but develop specific antibodies which can lead to severe hemolytic reactions during subsequent transfusions.

- **Transfusion associated circulatory overload (TACO)** due to rapid or large volume blood product transfusions may develop within 12 hours of transfusion, specially in children with pre-existing liver, heart or renal disease. TACO presents with sudden onset of dyspnea, pedal edema and hypertension and must be treated as an emergency with immediate discontinuation of transfusion, supplemental oxygen if needed, and diuretics.
- **Transfusion transmitted infections (TTI)** continue to be an important risk of blood product transfusions despite stricter quality checks and donor screening strategies. Apart from bacterial contamination, many viruses, e.g. HIV, HBV, HCV, etc. and protozoal infections, e.g. malaria, may be transmitted via blood product transfusions.

19.15.2 HEMATOPOIETIC STEM-CELL TRANSPLANTATION

The term hematopoietic stem-cell transplantation (HSCT) denotes replacement of abnormal or deficient pluripotent stem cells *or* progenitor hematopoietic cells with normal cells from same or different donor.

As bone marrow is the commonest source of normal stem cells for this purpose, the term Bone-marrow transplantation (BMT) is frequently used interchangeably with HSCT. However, stem cells may also be obtained from: (a) peripheral blood, (b) umbilical cord, (c) fetal liver.

Types: According to the source, HSCT/BMT may be classified as:

- *Autologous*, i.e. use of patient's own bone-marrow or stem cells, which is aspirated, treated with ablative chemotherapy, preserved, and at a later date, re-transfused into him.
- *Allogenic*, i.e. use of bone-marrow or stem cells from a HLA-matched donor, who may be either a non-identical but histocompatible related sibling *or* unrelated donor from donor registry.

Indications: HSCT is one of the most effective and potentially curative interventions in many hemato-oncological disorders. Currently it is the treatment of choice in:

- *Aplastic anemia:* Congenital or acquired
- Hemoglobinopathies, e.g. thalassemia
- *Refractory/relapsed leukemia:* ALL, AML
- *Lymphomas:* Hodgkin and NHL
- *Refractory/high-risk solid tumors:* Wilms tumor, neuroblastoma
- Inherited immunodeficiency disorders
- *Inborn errors of metabolism:* Gaucher disease, MPS, osteopetrosis

Principle: Although specific details of HSCT are beyond the scope of this book, general principles involves following steps:

a. Identification of donor and HLA cross-matching with recipient;
b. Pre-transplant conditioning of recipient to eradicate residual malignant cells and provide sufficient immunosuppression to facilitate engraftment of donor stem cells. Chemotherapy and total body irradiation is used for this purpose.
c. Harvesting, cryopreservation and storage of donor stem cells from bone marrow or peripheral blood;
d. Infusion of donor stem cells into recipient;
e. Post-HSCT immunosuppressive therapy to prevent graft rejection. Prophylaxis of opportunistic infections, nutritional supplementation and infection prevention is equally important.

Immunization of HSCT donors and recipients before the procedure and of recipient immunization after transplant is an important issue, discussed in Ch 9.4.

Complications of HSCT are conventionally divided into early and late complications with first 100 post-procedure days as dividing period.

- ***Early complications*** (<100 days):
  - Opportunistic infection due to disease/therapy-related immunosuppression
  - Acute graft versus host disease
  - Iatrogenic, e.g. GIT upsets, hemorrhagic cystitis, mucositis, interstitial pneumonitis, etc.
- ***Late complications*** include:
  - *Iatrogenic:* growth failure, hypothyroidism, etc.
  - Chronic graft versus host disease
  - Second malignancies, e.g. lymphoma.

Graft versus host disease (GVHD) denotes activation of donor T-cells after engraftment in an immunologically compromised host, clinically presenting as:

- *Acute form* (within 100 days of BMT) characterized by local erythroderma, cholestatic jaundice and enteritis.
- *Chronic form* (after 100 days), manifesting as Sjogren's syndrome, SLE and scleroderma, lichen planus and biliary cirrhosis.

Immunosuppressive therapy for variable period is used for the prevention and treatment of GVHD.

19.15.3 HEMATOPOIETIC GROWTH FACTORS

Hematopoietic growth factors are glycoproteins, which play a major role in the proliferation, differentiation and survival of primitive hematopoietic stem and progenitor cells, as well in functional activation of some mature cells. These growth factors include erythropoietin (for RBCs), colony stimulating factors (G-CSF, GM-CSF and M-CSF and SCF) and interleukins $IL_{1–16}$ (for leukocytes) and thrombopoietin (for platelets).

Erythropoietin, an erythropoiesis stimulant, is produced by kidney and currently available as recombinant preparation for clinical use (SC 50–150 U/kg/alternate day). It is primary used in cases with decreased bone marrow activity despite presence of stem cells, e.g. (a) chronic renal disease, (b) apnea of prematurity, (c) anemia during cancer chemotherapy, (d) myelodysplastic disorders and (e) to stimulate HbF production in sickle cell anemia.

Graulocyte stimulating factors specially GM-CSF and G-CSF are also available in recombinant form for use in neutropenic cases (SC 5–10 mg/kg or 250 mg/m^2), like-(a) malignancy and chemotherapy, (b) aplastic anemia and (c) autologous bone marrow transplantation. However, side effects, e.g. bone pains and rashes are common.

Thrombopoietin: Thrombopoietin is a glycoprotein hormone produced in the liver and kidney which regulate the production of platelets. It stimulates the production and differentiation of megakaryocytes, the bone marrow cells that bud off large number of platelets. Two TPO-RAs, Eltrombopag and Romiplostim have been approved for treatment of ITP.

19.16 DISORDERS OF SPLEEN

Spleen is an encapsulated mass of *red pulp*, i.e. tortuous capillaries (cords of Billroth) and fenestrated splenic sinuses, surrounded by *white pulp* (periarterial lymphatic sheaths containing T and B lymphocytes). A marginal dendritic zone of antigen-presenting cells separates red pulp from white pulp. Spleen receives ~5–6% of cardiac output, of which ~90% passes through micropores between splenic cords to sinuses for filtration.

Important functions of spleen include:

- *Filtration*, i.e. removal of senescent, deformed or antigen coated cells, i.e. *culling*, from circulation and their destruction
- *Repair* of damaged RBCs and other cells by removal of intracytoplasmic inclusion bodies and other cell debris from RBCs, i.e. *pitting*
- *Reservoir* for extra platelets and factor VIII, released on splenic capsular contraction by adrenaline, when required.
- *Hematopoiesis* in early fetal life (<3–6 months) or postnatal extramedullary erythropoiesis in severe hemolytic anemia.
- *Immunological* function, i.e. synthesis of IgM, properdin and *Tuftsin*-a phagocyte promoting tetrapeptide.

19.16.1 SPLENOMEGALY

Spleen is normally palpable in ~15% babies during first 3 months of life. Otherwise, the spleen must enlarge to at least 2–3 times of its size before being palpable clinically. Sub-clinical splenomegaly may be identified by USG, CT scan or ^{99m}Tc sulfur colloid scan, last one is also useful to assess splenic function.

Clinically palpable spleen should be differentiated from other common left hypochondriac mass, i.e. kidneys on the basis of—(a) direction of enlargement towards right iliac fossa, (b) movement with respiration, (c) presence of splenic notch, (d) inability to insinuate fingers below the rib-cage, and (e) absence of colonic band of resonance.

Palpable spleen may be graded according to its size either in terms of actual measurements or as per *Hackett's classification* **(Fig. 19.13)**. The size of spleen does not indicate its functional status and splenomegaly may be associated with hypersplenism, normal splenic functions or hyposplenism.

Etiology: Splenomegaly may be infective, congestive, hemolytic and infiltrative in origin **(Table 19.32)**. While mild splenomegaly is common in many systemic infections or diseases, *chronic malaria, hemolytic anemias and portal hypertension* are three leading causes of moderate/severe splenomegaly in Indian children.

Etiological differentiation between these cases depend on the age of presentation, epidemiological prevalence of common causes, size of splenomegaly and co-existing features, e.g. anemia, jaundice, hepatomegaly fever, portal hypertension, etc **(Table 19.33)**. Important diagnostic features of some common disorders with splenomegaly are as follows:

- ***Infective splenomegaly*** is the leading cause of splenomegaly, usually associated with history of fever. Malaria is the commonest cause of moderate/severe splenomegaly in Indian children, though kala-azar is common in certain Indian states, e.g. Bihar and eastern Uttar Pradesh. Mild transient splenomegaly is common in many bacterial and viral infections, including enteric fever and septicemia. Possibility of infective endocarditis should be considered in a child with co-existing heart disease.
- ***Congestive splenomegaly*** *(Banti syndrome)* is seen in portal hypertension and spleno-portal venous malformations. These cases usually present with gross splenomegaly and other signs of portal hypertension or hepatic disease, though hepatomegaly

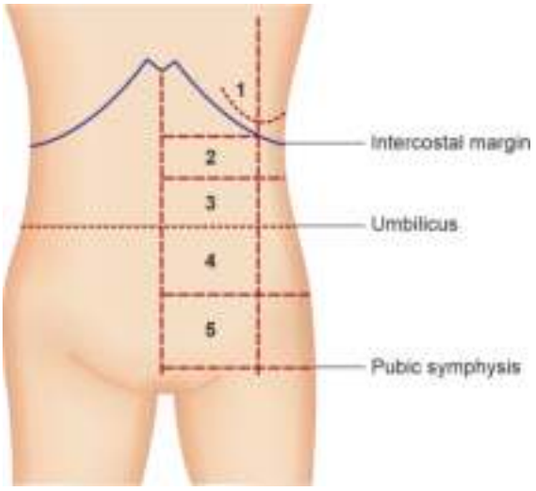

Fig. 19.13: Hackett's classification (numbers indicate severity grading of splenomegaly).

TABLE 19.32: Causes of splenomegaly

- **Infections**
  - *Parasitic:* Malaria, kala-azar
  - *Bacterial:* Typhoid, septicemia, Inf. endocarditis
  - *Tubercular:* Diss.TB
  - *Viral:* Inf. mononucleosis, CMV
  - *Spirochetal:* Leptospirosis
  - *Intrauterine:* CMV, toxoplasmosis, rubella
- **Hemolytic:** Hemolytic anemia, iron deficiency
- **Congestive:** Portal hypertesion, CCF
- **Neoplastic (Infiltrative)**
  - *Malignant:* Leukemia, lymphoma, secondaries
  - *Benign:* Hemangioma/hamartoma
  - Histiocytosis
- **Metabolic storage:**
  - Lipid storage disorders, e.g. Gaucher disease
  - Mucopolysaccharidosis
  - Glycogen storage disorders
- **Others:** Cysts, collagen disorders, e.g. SLE, JRA

TABLE 19.33: D/D of common causes of gross splenomegaly

	Chronic malaria	***Hemolytic anemia***	***Portal hypertension***	***Leukemia***	***Storage disorders***
History					
Age at diagnosis	Post-infancy	Infancy	Post-infancy	Any	Infancy
Demography	Endemicity	Caste/Family history	–	–	–
Assoc. history	Fever	Transfusions	Icterus/Umb. sepsis	–	Hypoglycemia
Examination					
Spleen size	+/++	+++	++	++	+++
Hepatomegaly	+	++	+	++	+++
Jaundice	–	+	+	–	–
Anemia	++	+++	+	++/+++	+/++
Others	–	Hemolytic face	Ascites, varices	Bleeding, LN	MR, FTT
Investigation	PS	PS	USG	PS	Liver biopsy

LN: Lymphadenopathy, **MR:** Develop/mental retardation, **FTT:** Failure to thrive, **PS:** Peripheral smear examination

is uncommon. History of perinatal infection and umbilical catheterization should always be asked in these cases. Splenectomy or portocaval anastamosis along with treatment of primary cause may be necessary in these cases.

- ***Hemolytic splenomegaly*** is characterized by coexisting hepatomegaly, anemia and often, mild icterus. Hereditary spherocytosis and thalassemia are two most important hemolytic anemias in children with gross splenomegaly. Unlike thalassemia, severe anemia requiring blood transfusions is uncommon in hereditary spherocytosis. In another common hemolytic anemia, i.e. sickle cell anemia, spleen is enlarged in earlier years but usually regresses by late childhood due to autosplenectomy.
- ***Infiltrative splenomegaly*** in neoplastic disorders, e.g. leukemia and lymphoma, is frequently associated with hepatomegaly, anemia and lymphadenopathy, along with other signs of malignancy, e.g. bone pains and weight loss. Rare causes of infiltrative splenomegaly include storage disorders, e.g. Gaucher's disease.

Some important clinical problems related to enlarged or hyper-functioning spleen are as follows:

Tropical splenomegaly is a unique problem in children and adolescents of developing countries, characterized by *"persistent moderate to severe splenomegaly of unknown etiology, with anemia and malnutrition"*. Occasionally, evidences of hypersplenism may also be present.

Etiologically, it is usually considered as an *abnormal immune response to chronic infections*, e.g. malaria, due to following reasons—(a) high incidence in malaria endemic regions, (b) frequent elevation of anti-malarial IgG titers, (c) regression in splenic size after anti-malaria therapy in some cases, and (d) declining incidence after relative control of malaria. However, a direct evidence, e.g. parasite in splenic puncture, is often absent. Recent evidences have shown non-cirrhotic portal fibrosis with portal hypertension in some cases.

Management is non-specific, though a trial of prolonged anti-malarial therapy (PO chloroquine 5 mg/kg/week for 6–8 weeks) is often effective in reducing the splenic size in endemic area. Very large splenomegaly or presence of portal hypertension may need splenectomy or portocaval shunt surgery.

Hypersplenism is a clinical complex, characterized by:

- Gross splenomegaly, due to any cause,
- Pancytopenia or bicytopenia, due to excessive cellular destruction in spleen,
- Correction of hematological abnormalities after splenectomy.

Hypersplenism, though nearly always secondary, may or may not respond to treatment of primary cause and splenectomy is necessary in non-responders.

Splenic injuries in children are uncommon unless it is markedly enlarged, and usually caused by blunt abdominal trauma.

Clinically, depending on the size of capsular tear, these cases present with—(a) left hypochondriac or shoulder pain (referred due to peritoneal irritation), (b) hypovolemia, and (c) shock due to massive internal hemorrhage. *Cullen sign*, i.e. peri-umbilical hyperpigmentation due to hemoperitoneum, is uncommon in children.

Diagnosis may be confirmed by USG/CT scan and ^{99m}Tc sulfur colloid scan.

Treatment depends on severity of intra-abdominal bleeding and circulatory status. Close hemodynamic monitoring, serial Hb estimations and blood transfusions as necessary, is all that is required in most cases, which heal spontaneously in 10–14 days. Emergency partial/total splenectomy is needed in severe cases.

19.16.2 HYPOSPLENIC STATES

Hyposplenism is a state of splenic dysfunction, due to—(a) congenital asplenia, (b) splenectomy, and (c) functional hyposplenism despite normal/enlarged spleen, as seen in sickle cell disease storage disorders, severe malaria and left quadrant radiotherapy.

Clinically, overwhelming infections, usually due to encapsulated organisms, e.g. pneumococci, *H. influenza* and Salmonella, etc. are very common in these cases.

Diagnosis: Peripheral smear in hyposplenic states reveals presence of characteristic intraerythrocytic inclusion bodies (*Howell-Jolly bodies or Heinz bodies)*, as well as target cells, hemosiderin granules and increased number of spherocytes. Diagnosis may be confirmed by Tc^{99m} sulfur colloid scan.

Management: All cases with hyposplenism should receive: (a) penicillin prophylaxis (PO 125–250 mg BD) for minimum 2 years or till 6 years of age, and (b) vaccination with *H. influenzae*, pneumococcal and meningococcal vaccines.

Splenectomy is *indicated* in cases of: (a) splenic rupture/trauma, (b) severe hemolytic anemia, e.g. hereditary spherocytosis, thalassemia, (c) secondary hypersplenism, (d) chronic/refractory immune thrombocytopenia (ITP), (e) metabolic storage disorders, (f) anatomical defects, e.g. cysts, and (g) rarely for surgical purpose *or* staging of Hodgkin disease.

As the risk of serious infections due to encapsulated organisms is very high in splenectomized children, splenectomy should be done only if inevitable, preferably postponed till 5–6 years of age. All splenectomized babies should receive penicillin prophylaxis (PO 125–250 mg BD for minimum 2 years or till 6 years of age) and vaccinations against *H. influenzae*, pneumococcal and meningococcal infections, as discussed earlier.

Splenosis is heterotopic autotransplantation of splenic tissue onto the peritoneum during splenectomy with subsequent growth. *Absence of Howell-Jolly bodies after splenectomy indicates possibility of splenosis*, which may be protective against infections, to some extent.

Congenital asplenia, i.e. *absence of spleen* is usually associated with complex cyanotic CHDs, dextrocardia and heterotopic abdominal organs. Unexplained recurrent infections with capsular organisms and typical peripheral smear abnormalities are strong indicators of asplenia in children, which may be confirmed by ^{99m}Tc sulfur colloid scan. These cases should be managed with penicillin prophylaxis and vaccinations against capsular organisms, discussed earlier.

Polysplenia or accessory spleen is present in ~10–15% population, usually near the hilum of main spleen or tail of pancreas and often detected accidentally during surgery/autopsy. Although of little significance *per se*, polysplenia may be associated with cardiac defects, left-sided organ defects and biliary atresia.

19.17 DISORDERS OF LYMPHATIC SYSTEM

The lymphatic system includes peripheral lymphocytes, lymphatic vessels and central lymphoid tissue, i.e. lymph nodes, spleen, tonsils, adenoids, Peyer's patches and thymus.

Lymph is an ultra-filtrate of blood (which oozed out into interstitial spaces) with a composition between transudate and exudate and contains variable number of lymphocytes. It is typically milky in color (*Chyle*) due to presence of fat globules, except in early neonatal period before the feeding is established. From interstitial spaces, lymph is carried by tiny lymphatic capillaries (except in heart and brain) to drain into proximal lymphatic channels interspersed with regional lymph nodes, and finally to reach venous circulation directly or via thoracic duct that opens in left subclavian vein.

Lymph nodes, consisting of well-defined dilated sinusoids lined by retiuloendothelial elements and surrounded by actively proliferating lymphocytes,

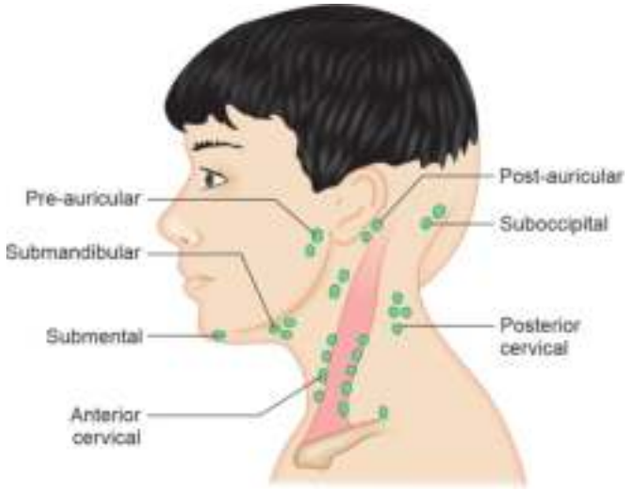

Fig. 19.14: **Normal anatomy of cervical lymph nodes.**

TABLE 19.34: D/D of generalized lymphadenopathy

Physiological	Normal lymphoid growth (4–8 years)
Reactive	Regional inflammatory lesions
Infective	
Bacterial	Typhoid, Plague
Tubercular	TB, atypical mycobacteria
Viral	HIV, Inf. Mononucleosis, CMV, measles
Others	Toxoplasmosis, histoplasmosis
Neoplastic	
Primary	Lymphoma (Hodgkin/non-Hodgkin)
Secondary	Leukemia, solid tumor metastasis
Infiltrative	Histiocytosis, Gaucher disease
Autoimmune	JRA, SLE, Kawasaki disease, ALPS
Drug-induced	Phenytoin

ALPS: Autoimmune lymphoproliferative syndrome

provide primary protective barrier against spread of regional infection. In sinusoids, lymph is filtered and particulate matters as well as living/dead organisms are phagocytised, processed and presented to further immune destruction.

According to location, lymph nodes are often termed as superficial (cervical, axillary, inguinal) or deeper (mediastinal, abdominal) groups.

Most frequently affected cervical group is divided into—(a) superficial *horizontal chain* or *external Waldeyer ring*, i.e. submental, submandibular, preauricular, post-auricular and suboccipital groups, (b) superficial *vertical chain*, i.e. anteromedial and posterolateral groups divided by sternocleidomastoid muscle **(Fig. 19.14)** and (c) deeper cervical lymph nodes.

Some common disorders of lymph nodes or lymphatic channels are as follows:

Lymphadenopathy: Being the primary protective barrier against infection, lymph nodes are affected in many regional infections and systemic disorders.

Examination of superficial lymph nodes is an integral part of general examination and finding should be denoted in terms of: (a) *size,* (b) *location or distribution,* (c) *consistency,* (d) *signs of inflammation,* e.g. tenderness, overlying erythema, etc. (e) *secondary changes*, e.g. matting, fluctuation, sinus formation, scrofuloderma, etc. and (f) presence of any *infective/inflammatory focus* in draining area.

Deeper lymph nodes, i.e. mediastinal or abdominal lymph nodes may be assessed on chest skiagram and USG/CT respectively.

Etiology: Lymphadenopathy may be physiological or pathological **(Table 19.34)**.

Pathological lymphadenopathy is indicated by—(a) size >1 cm (>1.5 cm in inguinal region), (b) involving multiple groups/regions, (c) firm/hard or fluctuating in consistency, (d) associated with secondary changes, and (e) presence of regional infective pathology.

Some typical features in common causes of lymphadenopathy in India are as follows:

- ***Physiological lymphadenopathy*:** Superficial lymph nodes may be normally palpable, specially between 4–8 years of age (i.e. period of normal lymphoid growth) and regress subsequently.
- ***Reactive lymphadenitis*** due to infective/inflammatory lesions in drainage area is localized, tender and transient, lasting for a few days. Streptococcal sore throat and viral pharyngitis are leading causes of unilateral and bilateral cervical lymphadenopathy, respectively.
- ***Tubercular lymphadenopathy*** is the commonest cause of persistent lymphadenopathy in Indian children, usually involving cervical or axillary nodes. Nodes are infected via lymphatic spread from intrathoracic nodes (natural infection) or vaccine site. BCG lymphadenitis is the commonest cause of axillary lymphadenitis in infancy (Ch 9.2).

  Tubercular lymphadenopathy is characterized by *firm, non-tender and matted nodes* with/without secondary changes, e.g. *sinus formation* and *scrofuloderma*, i.e. exudative crusted skin lesions surrounding the sinus **(Fig. 19.15)**.
- ***Neoplastic lymph nodes*** are typically non-tender, firm, fixed to skin/underlying structures, rapidly enlarging and/or involving multiple groups. In Hodgkin's disease, nodes typically have *India-rubber* consistency.

Diagnostic evaluation of lymphadenopathy is best achieved by fine needle aspiration cytology (FNAC) or lymph node biopsy, though supportive investigations, e.g. peripheral smear (for malignancy, infectious mononucleosis, etc.), tuberculin test and chest skiagram (for TB) and serology for other infections may clinch the diagnosis in many cases. In generalized

Fig. 19.15: **Tubercular lymphadenopathy.**

lymphadenopathy, it is also essential to evaluate status of deeper nodes by USG/CT scan.

Lymph node biopsy is indicated in: (a) clinically pathological lymph nodes, (b) presence of constitutional signs, e.g. fever, weight loss, etc., (c) increasing size for >2 weeks, and (d) no decrease/resolution in 6–8 weeks, despite antibiotics.

Lymphangitis is a regional inflammation of the lymphatic channels, presenting as tender-red streaks that extend proximally from infected site with enlarged and tender regional nodes. *Staph. aureus* and *Group A β hemolytic streptococci* are commonest organisms responsible for acute lymphangitis.

Lymphedema denotes obstruction of lymphatic flow, either due to congenital causes (Turner syndrome, Noonan syndrome, Milroy disease) or acquired pathology in regional lymph nodes, e.g. filariasis, neoplasms, post-radiation or post-inflammatory scarring.

Cystic hygroma is a thin-walled, soft, fluctuant and brilliantly transilluminant cyst, filled with clear fluid, representing a lymphangioma or sequestered portion of embryonic jugular lymph sac. These swelling are present at birth or manifest in early infancy, most common in posterior triangle of neck. Compression of neighboring vital structures *or* cyst infections are important complications of cystic hygroma.

USG helps in antenatal and postnatal confirmation of cystic hygroma (multi-loculated echolucent mass). Treatment is surgical, with excision of as many cysts as possible while preserving vital structures, though laser therapy and sclerotherapy may be used for lesions not amenable to excision.

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CHAPTER 20

Oncological Disorders

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Malignancy is the ninth leading cause of childhood morbidity globally. In India, children account for <1% of all reported cancer patients with an estimated incidence of ~14/lac children, which seems to be rising. Childhood malignancies differ markedly from adult cancers in their nature, distribution and prognosis.

20.1 BASIC CONSIDERATIONS

Acute leukemia, lymphomas and brain tumors are most common malignancies in childhood, accounting for ~60–80% of all cancers in this age group with minor age-wise differences **(Table 20.1)**. Brain tumors are commonest non-hematological solid neoplasms in children, though most of them are benign or low-grade malignancies.

Amongst others, tumors of embryonal tissue, e.g. neuroblastoma, Wilms' tumor, retinoblastoma and hepatoblastoma are more common in infancy and early childhood, while bone or soft-tissue sarcomas and gonadal tumors dominate in adolescents. Malignancy is rare in newborns, commonest being undifferentiated leukemia, neuroblastoma, sacrococcygeal teratoma, retinoblastoma and Wilms tumor.

General Concepts in Etiology

Malignancies denote *unregulated growth of normal or abnormal tissue*. Precise mechanisms for this dysregulation is not well established in most cases, though probably relate to two factors-*Genetic* predisposition and adverse *Environmental* influences.

TABLE 20.1: Age-wise occurrence of common neoplasms

	<5 years	*5–9 years*	*9 years*
Leukemia	36%	31%	18%
Lymphoma	10%	25%	25%
Brain tumors	13%	25%	18%
Renal tumors	10%	5%	Rare
Bone tumors	Rare	Rare	18%
Neuroblastoma	7%	3%	Rare
Soft tissue tumors	Rare	5%	5%
Others	24%	6%	26%

Genetic factors: Normal or abnormal cell growth is regulated by two types of genes-*Proto-oncogenes*, which promote cell growth, and *anti-oncogenes* or tumor suppressor genes, which regulate the functions of protooncogenes. Any event, which alters the balance between proto-and anti-oncogenes may cause cancers. Some well-known examples are:

- Activation of proto-oncogenes, e.g., neuroblastoma or non-Hodgkin's lymphoma.
- Disruption of tumor suppressor genes, e.g., retinoblastoma.
- Creation of fusion genes, e.g., Ewing's sarcoma.
- Chromosomal abnormalities, e.g., trisomies (leukemia), deletions (Wilms' tumor) or translocations, e.g., Burkitt's lymphoma or chronic myeloid leukemia.
- Fragile chromosomes with excessive tissue breakdown, e.g. Bloom syndrome, Fanconi's anemia.

Genetically predisposed malignancies tend to be familial, early-onset and usually bilateral. Pediatric malignancies are more likely due to genetic factors, arising from tissues which are not directly exposed to environment, e.g. blood, brain, etc. Second malignancies are common in these cases.

Environmental factors may act directly or by uncovering an underlying genetic error. Some common adverse environmental factors are:

- *Physical* agents, e.g., ionizing/ultraviolet radiation.
- *Chemical* agents, e.g., smoking, tobacco, drugs, etc.
- *Toxins*, e.g., asbestos (mesothelioma), pesticides, etc.
- *Infections*, e.g. HBV, HCV, EBV, Papova virus, etc.
- *Dietary* factors, e.g. low-fiber diet (colon cancer).

Malignancies due to environmental factors are more common in adults, tend to be unilateral and non-familial, arising from tissues which are directly exposed to environment, e.g., lungs, oral cavity, gut or genitourinary tract.

General Clinical Indicators

Clinical manifestations of childhood malignancies vary according to the type, site and extent of disease, though important warning signals include:

a. *Unexplained hematological abnormalities*, e.g., anemia, thrombocytopenia and leukopenia or leukocytosis.
b. *Unexplained masses or swellings*, e.g., abdominal mass, mediastinal mass, lymphadenopathy or soft-tissue swellings.
c. *Unexplained systemic features,* e.g., failure to thrive, prolonged pyrexia, diarrhea, bone pains, organomegaly, hypertension, neurological defects.
d. *Miscellaneous signs*, e.g., leukocoria, exophthalmos, opsoclonus, etc.

General Principles of Diagnosis

Diagnosis of malignant disorders usually rests on histopathological studies in biopsy specimens or blood, supplemented by immunological and cytogenetic studies to appreciate the etiological basis, decide the treatment plan and predict the outcome. Genetic studies also help to predict the risk of some malignancies in siblings and other family members of a child with malignancy.

Each case also needs thorough search for local and/or metastatic spread of disease (staging of the disease) by appropriate radioimaging, nuclear or PET scans and if necessary, aspiration/biopsy from the suspected site of spread, e.g., lymph nodes or bone marrow.

General Principles of Management

Management of cancers is a team work, best handled by experts, e.g. pathologists, medical oncologists, surgeons, radiotherapists, psychologists and ancillary staff, including nurses. Broadly, it may be divided into three components:

a. **Specific therapy** involves surgery, chemotherapy, radiotherapy and immunotherapy, depending on the histopathological type, location, extent and character of tumor. Standard guidelines are available for management of specific tumors, discussed in respective chapters, though more effective and less toxic protocols are evolving.
   – ***Conventional chemotherapeutic agents*** for malignancy generally include—(a) *Antimetabolites*, e.g., methotrexate, 6 mercaptopurine, cytarabine, (b) *akylating agents*, e.g., cyclophosphamide, ifosfamide, (c) *antibiotics*, e.g., doxorubicin, daunomycin, bleomycin, (d) *vinca alkaloids*, e.g., vincristine, vinblastin, (e) *enzymes*, e.g. L-asparaginase, and (f) *others,* e.g., etoposide.
   – ***Biological agents***, e.g. immunotherapy, biological response modifiers or endogenously occurring molecules are being increasing used in management of cancers. Common examples include *retinoic acid* in acute promyelocytic leukemia, *monoclonal antibodies*, e.g. anti-GD2 antibody in neuroblastoma and non-Hodgkin lymphoma, *tyrosine kinase inhibitors*, e.g. imatinib mesylate in chronic myelogenous leukemia, etc.
   – ***Molecular targeted therapy:*** Recognition of molecular mechanisms in cancer process has led to development of specific antineoplastic therapies, with advantage of minimum toxicity to normal tissues unlike conventional drugs. Many of the new biologic agent therapies, such as imatinib and rituximab, fall into this category.
b. **Supportive therapy** with adequate nutrition, fluid and electrolyte balance, prevention of infections and other complications, as well as psychological support.
c. **Management of emergencies:** Oncological emergencies may be tumor-specific or non-specific and may be present at the time of diagnosis or arise during the course of therapy **(Table 20.2)**, some of them are as follows:
   – ***Tumor lysis syndrome (TLS)*** is a triad of—(a) hyperuricemia, (b) hyperkalemia, (c) hyperphosphatemia with/without hypocalcemia, due to rapid release of intracellular metabolites at a rate that exceeds renal excretory capacity.

     TLS is common in bulky tumors, e.g. lymphomas, or soon after initiation of chemotherapy due to rapid cell necrosis and should be anticipated in a case with-(a) poor urine output, and (b) elevated LDH and uric acid levels.

     Prevention of TLS involves: (a) adequate hydration (minimum 3000 ml/m^2/day) with/without diuretics, (b) alkalinization of urine with $NaHCO_3$ (50–75 mEq/L) to increase uric acid excretion and (c) allopurinol therapy (PO 10 mg/kg/day).
   – ***Hyperleukocytosis,*** i.e. TLC >1,00,000 cells/mm^3), is seen in 5–20% of acute leukemia, leading to: (a) TLS, (b) *CNS leukostasis* with headache, seizures or papilledema, (c) *pulmonary leukostasis* with dyspnea or corpulmonale, (d) *peripheral leukostasis*, e.g. priapism or gangrene.

     These cases need aggressive hydration, alkalinization of urine, allopurinol and partial exchange/leukopheresis.
   – ***Superior vena caval syndrome*** (SVCS) is an indicator of SVC compression due to mediastinal tumors, usually seen in lymphomas and neuroblastoma.

     SVCS present with signs of: (a) tracheal compression, e.g., persistent cough, dyspnea or stridor, (b) SVC compression, e.g., facial edema/cyanosis, conjunctival suffusion, neck veins engorgement and prominent chest collaterals, (c) vagal/recurrent laryngeal nerve compression, e.g. hoarseness of voice, and (d) esophageal compression, e.g. dysphagia. These cases may evolve in few hours and signs are more prominent in flexed-neck position.

TABLE 20.2: Important oncological emergencies and their management

Complications	*Causes*	*Treatment*
a. Infections		
Nosocomial infections	Diagnostic / therapeutic procedures	Asepsis, antibiotics
Opportunistic infections	Chemotherapy, BM* suppression	Antibiotics
b. Hematological		
Severe anemia	Hemorrhage, BM* involvement	Packed cells transfusion
Bleeding/thrombocytopenia	BM* involvement	Platelets transfusion
Neutropenia	BM* involvement	Antibiotics, G-CSF
DIC	Sepsis, tumor factors	Plasma, platelets, heparin
Thromboembolic episodes	Leukostasis, vaso-occlusion	Partial exchange, leukapheresis
c. Mechanical		
Raised intracranial pressure	Brain tumor/metastasis	Steroids, shunt, anticonvulsants
Superior vena cava syndrome	Mediastinal mass	Radiotherapy, steroids
Spinal cord compression	Spinal mass	Radiotherapy, steroids, laminectomy
d. Metabolic		
Hyperuricemia	Tumor lysis syndrome	Hydration, urine alkalinization, allopurinol
Hyperphosphatemia	Tumor lysis syndrome	Diuresis, oral Al $(OH)_3$, stop alkalinization
Hyperkalemia	Tumor lysis syndrome	$NaHCO_3$, insulin, exchange resins
Hypercalcemia	Bone metastasis	Hydration, steroids, mithramycin, diphosphates
Hyponatremia	SIADH	Fluid restriction, Na^{++} supplements
e. Systemic complications		
Hepatotoxicity	Liver metastasis, drugs	Supportive, stop toxic drug
Nephrotoxicity	Drugs	Supportive, stop toxic drug
Skin lesions	Drugs	Supportive, stop toxic drug
f. Late sequelae		
Pulmonary dysfunction	Drugs, radiation	–
Leukoencephalopathy	Radiation, drugs	–
Endocrinal dysfunction	Drugs, radiation, surgery	–
Sterility/ infertility	Drugs, radiation, surgery	–
Secondary cancers	Drugs, radiation	–
Deformities	Surgery	–

***BM:** Bone marrow

Immediate diagnosis with CT/MRI and empirical radiotherapy with/without steroids may be life-saving before definite diagnosis.

20.2 LEUKEMIA

Leukemia is the commonest pediatric malignancy, accounting for ~1/3rd of all cancers and defined as *"malignant clonal proliferation of lymphoid or myeloid precursor cells in bone marrow as well as infiltration of other organs with these cells"*.

Depending on the predominant cell line and presentation, these cases are sub-classified as *acute lymphoblastic leukemia* (ALL), *acute myelogenous or non-lymphoblastic leukemia* (AML), *chronic myelogenous leukemia* (CML) and *juvenile myelomonocytic leukemia* (JMML).

ALL is the commonest leukemia in children (77%), followed by AML (11%), CML (2–3%) and JMML (1–2%). Some remaining cases do not fit classical definition of the any type.

20.2.1 ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Childhood ALL is considered as the prototype for cancer research, being the first disseminated malignancy cured by chemotherapy and irradiation. Currently, ~70–80% of these cases are potentially curable.

Epidemiology: Incidence of ALL is estimated to be ~3–10/lac population; being 3–4 times more common in males. Peak age incidence is between 3–7 years.

Etiology: While exact etiology is not known, important hypotheses suggest:

- *Genetic basis,* due to higher risk in twins or siblings of index case (3–4 times) or in many genetic syndromes (10–20 times), e.g. Down syndrome, Bloom syndrome, Fanconi's anemia, neurofibromatosis and congenital immunodeficiency disorders, e.g. agammaglobulinemia or ataxia telangiectasia. Chromosomal abnormalities, e.g. aneuploidy or translocations are present in >80% of leukemic cells. Many germline single nucleotide polymorphisms have been identified with higher risk of ALL, involving genes like ARID5B, IKZF1, etc.
- *Environmental basis,* due to occurrence of many cases in geographical clusters or as second malignancy after radiotherapy or chemotherapy. Exposure to pesticides, pains and other chemicals as well as heavy paternal smoking in periconceptional period has also been implicated in higher risk of ALL.

Pathology: ALL is characterized by increased number of lymphoblasts in bone marrow *with or without* their presence in peripheral blood or infiltration to other organs.

A ***lymphoblast*** is characterized by:

- *Typical morphology*, i.e. high nucleus-cytoplasm ratio, dense nuclear chromatin and basophilic nongranular cytoplasm **(Fig. 20.1)**,
- *Cytochemical characteristics*, i.e. presence of coarse granules/clumps on PAS staining, absence of peroxidase or Sudan-black positive granules and nonspecific esterase reaction,
- *Biological markers*, e.g. presence of terminal deoxynucleotidyl transferase (TdT) activity in B-progenitor and T-cell lymphoblasts, which is absent in normal lymphocytes.

Classification: ALL is classified according to lineage of blast cells and presence of immunological markers, as per WHO classification **(Table 20.3)**. A small percentage of cases have markers for both lymphoid and myeloid derivation. In addition, chromosomal abnormalities are also used to classify the disease, for the purpose of treatment and outcome.

Clinical presentation: Initial symptoms are generally nonspecific and mimic a viral infection, e.g., fever, anorexia and lethargy. Nearly 2/3rd of cases present within 4 weeks of onset of symptoms with:

- *Signs of primary bone marrow failure*—pallor, fever or persisting/recurrent infections (leukopenia) or mucocutaneous bleeding (thrombocytopenia)
- *Signs of secondary organ infiltration*—mild lymphadenopathy, splenohepatomegaly, bone/joint pains (due to perichondrial bone infiltration and subperiosteal bleeds) and headache/vomiting (due to meningeal involvement).
- *Signs of mediastinal mass*, e.g. SVC compression, dysphagia and dyspnea, more common in T-cell leukemia.

Diagnosis is usually suggested by presence of lymphoblasts in peripheral smear and confirmed by *bone marrow examination* for complete morphological, immunological and cytogenetic studies.

Hematologically, severe anemia is present in 25% and thrombocytopenia in 75%. In childhood ALL, leukopenia is more common than leukocytosis.

Other investigations are necessary to identify secondary organ infiltration or as pre-treatment workup for monitoring and dose adjustments for chemotherapy **(Table 20.4)**.

D/D of ALL includes other causes of—*(a) bone-marrow failure*, e.g., aplastic anemia, infiltrative diseases, metastasis from other malignancies, *(b) atypical lymphocytosis*, e.g., infectious mononucleosis or pertussis, and *(c) splenohepatomegaly or lymphadenopathy.* Rarely, cases with bone/joint pains may be confused with other causes of arthritis.

TABLE 20.3: WHO classification of acute lymphoblastic leukemia

- B-Lymphoblastic leukemia (85%)
  (earlier termed PreB or early PreB ALL)
- T-Lymphoblastic leukemia (15%)
  (earlier termed T-cell ALL)
- Burkitt leukemia (<1%)
  (arising from mature B cells)

TABLE 20.4: Diagnostic work-up in leukemia

Screening: Peripheral smear for blast cells
Diagnostic: Bone marrow aspirate/biopsy
For severity/extent of disease:

- Blood profile for Hb, TLC, platelet count
- Chest X-ray for mediastinal mass, TB
- CSF exam for blast cells (CNS involvement)

Pre-treatment workup:

- Renal function test, including electrolytes
- Liver function tests
- Coagulation profile
- S. LDH, uric acid, calcium, phosphorus*
- Viral markers: HIV, HBV, HCV
- Echocardiography

*Tumor lysis profile

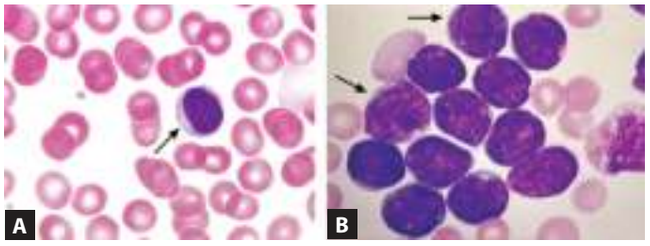

Fig. 20.1: **(A) Normal lymphocyte; (B) Lymphoblasts.**

Management includes—(a) specific treatment, (b) supportive treatment, and (c) monitoring, early diagnosis and treatment of relapse.

a. Specific treatment depends on clinically anticipated risk for relapse *(risk-based approach)*.

A *standard risk ALL patient* with average risk of relapse, is defined as—(a) age between 1–10 years, (b) female, (c) initial TLC <50,000/mm^3, (d) B-cell immunophenotype, (e) rapid response to chemotherapy with <0.01% minimal residual disease, i.e. burden of leukemic cells in bone marrow, on Day 33 of induction, (f) absence of mediastinal mass or CNS involvement, and (g) absence of hypodiploidy or other chromosomal abnormalities, e.g. translocations (t9:22 and t4:11) or fusion genes (BCR/ABL and MLL/AF4).

Standard-risk treatment revolves around multi-drug chemotherapy with various protocols, most commonly used one is given in **Table 20.5**. It may be divided into three phases: (a) *induction* phase for 4–6 weeks, (b) *consolidation and intensification* phase with CNS prophylaxis and systemic chemotherapy for 14–28 weeks, and then, (c) *maintenance* phase for next 2–3 years with intermittent reinforcement therapy.

1. ***Induction phase*** aims to eradicate leukemic cells from bone marrow, using weekly Vincristine, daily steroids and single dose of long-acting pegylated Asparaginase, for 4 weeks. Weekly Daunomycin is added in high-risk cases. By the end of 4 weeks, >98% cases achieve remission, i.e. <5% blast cells in marrow and normalization of peripheral cell counts. CNS prophylaxis, with intrathecal, methotrexate, hydrocortisone and cytarabine is given at the onset of treatment.

TABLE 20.5: Treatment regimen for standard risk ALL

• **Induction phase (for 4–6 weeks)**	
IV Vincristine	1.5 mg/m^2 (weekly; max 2 mg)
+ IM Asparginase	10,000 U/m^2 (bi-weekly)
+ PO Prednisolone	40 mg/m^2 (daily)
• **Intrathecal CNS prophylaxis (weekly during induction, than 8-weekly for 2 years)**	
IT Methotrexate	10–15 mg/m^2
+ IT Hydrocortisone	10–15 mg/m^2
+ IT Ara-C (cytarabin)	20–30 mg/m^2
• **Maintenance therapy (after induction phase, for 2 years)**	
PO 6-Mercaptopurine	50 mg/m^2 (daily)
+ PO Methotrexate	20 mg/m^2 (weekly)
• **Reinforcement therapy (every 4 weeks, during maintenance therapy)**	
IV Vincristine	1.5 mg/m^2 (single dose)
+ PO Prednisolone	40 mg/m^2 (for 7 days)

2. ***Consolidation and intensification phase*** begins once the remission has been achieved and is focussed on CNS prophylaxis with intrathecal chemotherapy (as above) along with continued intensive systemic chemotherapy, to eradicate the disease. Considering adverse effects on growing brain, cranial irradiation is used only in cases of documented CNS involvement with abnormal clinical signs, e.g. cranial nerve palsy or CSF finding, e.g. elevated cell counts.

   Systemic chemotherapy may continue with same drug-combination as used in induction phase or different drugs as per selected protocols. This phase usually lasts for 14–28 weeks and some protocols use a base-line interim maintenance along with intermittent phases of aggressive treatment (*Delayed intensification*).
3. ***Maintenance phase*** begins subsequently for 2–3 years, depending on the protocol used, using daily 6-Mercaptopurine and weekly Methotrexate (both orally), along with intermittent doses of IV Vincristine and steroids, usually every 4 weeks.

High-risk cases are treated with more intensified regimens, due to higher risk of relapse. *B-cell leukemia* (or L_3 morphology) is preferably treated with short but intensive regimens similar to those for advanced B-cell lymphoma. *T-cell leukemia* is best treated with Dexamethasone and intensive chemotherapy blocks.

b. Supportive treatment is required to manage complications of disease as well as chemotherapy and includes:

- Maintenance of adequate nutrition and hydration,
- Correction of fluid and electrolyte imbalance,
- Correction of severe anemia by packed cell transfusions,
- Correction of bleeding problems by platelet transfusions,
- Prevention, early diagnosis and treatment of nosocomial infections,
- Treatment of metabolic complications, e.g. hyperuricemia (Allopurinol),
- Monitoring and treatment of chemotherapy-related adverse effects, and
- Psychological support to patient and family.

c. Diagnosis and treatment of relapses: Common sites of relapses in ALL are—(i) bone marrow, (ii) CNS, and (iii) testes, also termed *sanctuary sites* for blast cells. Absence of a relapse for >2 years is usually considered as cure.

- ***Bone marrow relapse*** is the site of relapse in 15–20% cases, identified by periodic blood counts and peripheral smear examination and confirmed by bone marrow examination (>5 blast cells/HPF) during or after chemotherapy.

  Late bone marrow relapse (>18 months) is usually treated with reinduction therapy (similar to first attack but with different drugs) including CNS prophylaxis, followed by longer maintenance therapy.

Early relapsers (<18 months or during treatment) need more intensive chemotherapy followed by bone marrow transplantation.

- ***CNS relapse*** is relatively uncommon (<5%), after inclusion of CNS prophylaxis in all cases of ALL, indicated by: (a) signs of raised intracranial pressure, e.g., headache, vomiting and papilledema, (b) seizures or cranial nerve palsies, and (c) hypothalamic involvement, e.g., excessive weight gain or behavioral changes.

  Diagnosis rests on CSF examination showing elevated pressure, pleocytosis and presence of leukemic cells. *Even a single blast cell in CSF suggests CNS relapse.*

  These cases should be treated with—(a) weekly intrathecal chemotherapy till lymphoblasts disappear from CSF, followed by (b) cranial irradiation and preventive CNS therapy as in initial attack, and (c) simultaneous systemic chemotherapy, due to high risk of bone marrow relapse.
- ***Testicular relapse,*** occurs in <2% cases, presenting with painless swelling of one or both testicles, and confirmed on testicular biopsy.

These cases must be treated with—(a) irradiation of gonads and (b) simultaneous systemic chemotherapy including CNS prophylaxis as in first attack.

Prognosis: Overall cure rare in ALL is ~80%, though varies with *risk-status* of patient and adequacy of therapy. With current therapeutic regimens, cure rare is >90% for standard risk cases, ~50% for T-cell leukemia and ~20% in high-risk cases or B-cell leukemia.

Bad prognostic indicators include—(a) age <1 year or >10 year, (b) high leukocyte count (>50,000/mm^3), (c) mediastinal or CNS involvement, (d) presence of chromosomal abnormalities, mentioned earlier, and (e) delayed remission or early relapse on treatment.

20.2.2 ACUTE MYELOGENOUS LEUKEMIA

Acute myelogenous or non-lymphoblastic leukemia (AML or ANLL) accounts for ~15–20% of childhood leukemia.

Many of these cases are associated with genetic disorders, e.g. Down syndrome, Fanconi anemia, Bloom syndrome or neurofibromatosis, or develop as secondary malignancy after chemotherapy or radiotherapy for other malignancies.

Clinical presentation is similar to ALL, though most cases have more acute and severe course with higher incidence of severe anemia, bleeding and *chloroma*-a localized mass of leukemic cells on choroid and epidural region.

Acute promyelocytic type of AML is specifically associated with gum hypertrophy, gum bleeding or severe DIC, due to release of procoagulant substances from leukemic blast cells. Subcutaneous nodules (*blueberry muffins*) are common in infants.

TABLE 20.6: WHO classification* for acute myelogenous leukemia

AML/APL with recurrent genetic abnormalities
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, not otherwise specified
• With minimal differentiation
• With/without maturation
• Acute myelomonocytic leukemia
• Acute monoblastic/monocytic leukemia
• Acute erythroid leukemia
• Pure erythroid leukemia
• Erythroleukemia, erythroid/myeloid
• Acute megakaryoblastic leukemia
• Acute basophilic leukemia
• Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Blastic plasmacytoid dendritic cell neoplasm

*Modified and abridged.
AML: Acute myelogenous leukemia; **APL:** Acute promyelocytic leukemia

Diagnosis depends on presence of >20% myeloblasts in the bone marrow, though further differentiation is required from lymphoblasts on the basis of morphologic, immunophenotype and cytogenetic characters.

WHO recommends the classification for AML based on the morphology and chromosomal or genetic abnormalities **(Table 20.6)**.

Treatment regimens for AML are not as standardized as for ALL, though risk-stratification is possible on the basis of selected genetic abnormalities. Most protocols use an anthracycline (e.g. daunamycin) and cytosine arabinoside with/without other agents, e.g. etoposide. Addition of *retinoic acid (tretinoin)* to these protocols during induction phase has shown promising results in acute promyelocytic leukemia.

With current chemotherapeutic regimens, initial remission may be achieved in >80% cases, though relapses are common and bone marrow transplant is indicated majority of cases for best results.

Supportive therapy is very important in AML, as most cases are seriously sick on presentation and may die soon after hospitalization due to hemorrhage or overwhelming infections.

Prognosis: Overall cure rate is ~50% with chemotherapy alone and ~70% on chemotherapy with bone marrow transplant. AML with Down syndrome has more favorable prognosis, while bad prognostic factors include—(a) severe sepsis/bleeding on presentation, (b) secondary AML, and (c) early relapse. Cases with certain gene mutations in their leukemic cells, e.g. FLT3, NPM, etc. may have better or worse outlook.

20.2.3 CHRONIC MYELOGENOUS LEUKEMIA (CML)

CML accounts for ~3% of childhood leukemia and include two distinct types-*juvenile CML* and *adult CML*.

Juvenile CML (Now termed as *juvenile myelomonocytic leukemia*) presents in younger children <5 years of age, more common in those with neurofibromatosis and Noonan syndrome.

Clinically, most cases present with moderate to severe splenohepatomegaly, lymphadenopathy, skin lesions (eczema, xanthoma, *café au lait* spots) and signs of bone marrow failure, e.g. pallor and bleeding.

Pathologically, it is characterized by—(a) leukocytosis with striking monocytosis in peripheral smear, (b) increased cellularity with predominance of immature granulocytes in all stages, specially monocyte precursors in bone marrow, and (c) increased fetal hemoglobin levels.

Nearly all patients have a genetic lesion, with monosomy 7 in 30%. However, *Philadelphia chromosome (d/d adult CML) is absent* in these cases.

Treatment of choice is bone marrow transplant, as chemotherapy is not very effective. Even with transplant, 3 year survival rate is 30–50%.

Adult CML is rare in children (3–5% of all CML), characterized by presence of a specific chromosomal translocation, i.e. *Philadelphia chromosome* (t9;22–q34;11), resulting in presence of a BCR-ABL fusion protein.

Clinically, most pediatric cases present in second decade with a triphasic illness—(a) chronic phase for many years, with failure to thrive and gross splenomegaly, (b) accelerated progression phase, and (c) intermittent or terminal lymphoblastic/myeloblastic crisis.

Pathologically, these cases are characterized by—(a) presence of all types of immature myeloid cells in peripheral smear, (b) myeloid hyperplasia with myeloid blasts and promyelocytes in bone marrow, and (c) presence of *Philadelphia chromosome* on cytogenetic studies. *Thrombocytosis* is common.

Treatment during the chronic phase aims to control leukocytosis with *Imatinib* or other BCR-ABL tyrosine kinase inhibitors as preferred choice, which also retards progression to accelerated phase and reduce the risk of crisis. Acute lymphoid or myeloid crisis is treated with standard ALL or AML therapy. Periodic monitoring with bone marrow every 6 months is advised to assess residual disease or relapse. Bone marrow transplant may be used in non-responders or during accelerated phase.

20.3 LYMPHOMA

Lymphomas are third commonest malignancy in children (10–15%) after leukemia and brain tumors. These tumors may be broadly classified into two categories — *Hodgkin lymphoma* (HL) and *Non-Hodgkin lymphomas* (NHL) **(Table 20.7)**. In young or children, NHL is relatively more common than HL.

TABLE 20.7: Hodgkin vs non-Hodgkin lymphoma

	HD	*NHL*
% Childhood lymphoma	40%	60%
Age of presentation	Bi-modal*	Children
Sex preponderance	Equal	M > F (3:1)
Site of origin	Nodal	Extranodal
Metastasis	Slow	Rapid
Prognosis	Good	Poor

**See* text

20.3.1 HODGKIN LYMPHOMA (HL)

HL is a lymphoid malignancy of primarily nodal origin with B-cell lineage, accounting for ~40% lymphomas in children, with relatively slower and orderly spread of disease than in NHL.

Epidemiologically, HL is rare below 5 years of age, with a bimodal age distribution in western countries, at 15–35 years and then after 50 years. However, Indian children are frequently affected at younger age without sex difference, except slight male predominance in cases <10 years.

Etiology is multifactorial and important risk-factors include—(a) consanguinity or similar disease in family (suggestive of genetic basis), (b) preceding Epstein-Barr virus (EBV) infection, and (c) underlying immunodeficiency or autoimmune disorders, e.g. JIA or SLE.

Siblings of a case have 7-times higher risk of developing HL, which is 100-times more in monozygotic twins.

EBV infection increases risk of subsequent HL by 4-times and EBV-DNA has been found in *hallmark Reid-Sternberg cells.*

Pathologically, HL usually arises from cervical (70%) or mediastinal (20%) lymph nodes, though may begin from any other site or extranodal lymphoid tissue. *Presence of Reed-Sternberg cell* — a giant cell with mirror image nucleus, *is hallmark histological feature* of HL.

WHO classification of HL includes two major types–nodular lymphocyte predominance (NLPHL) and classic (cHL), with cHL including four subtypes-nodular sclerosing, mixed cellularity, lymphocyte predominance and lymphocyte depletion. Nodular sclerosing HL is the commonest HL globally (50%), followed by mixed cellularity (40%), though the later type is more common in India.

HL spreads via lymphatic channels to adjacent nodes or hematogenously to extra-lymphatic organs, e.g. liver, spleen, bone marrow, lungs and brain.

TABLE 20.8: Modified Ann Arbor staging system for HL

Stage	*Involvement of …*
I	Single LN region or EN site
II	Two or more LN regions or Nodal + EN involvement on same side of diaphragm
III	LN ± one EN involvement on both sides of diaphragm
-III1	Abdomen disease limited to upper abdomen
-III2	Abdomen disease involving lower/whole abdomen
IV	Disseminated involvement of one or more EL sites, with/without associated LN disease
Each stage is further sub-classified as	
A	No B symptoms
B	Presence of (any one) recurrent fever, Night sweats or unexplained weight
X	Bulky tumor >10 cm*
E	Localized EN extension from continuous nodal site

LN: Lymph node EN: Extranodal
*Or Mediastinal tumor > 1/3rd of transverse intrathoracic diameter

TABLE 20.9: Treatment plan and outcome in HL

Stage	*Treatment*	*Survival*
I, II, IIIa	LD-RT + Chemo (3-4 cycles)	> 90%
IIIb, IV	LD-RT + Chemo (> 6 cycles)	~ 60%
Relapse	Same as above/	~ 60%
	Anti-CD20 antibodies	
Treatment failure*	Bone marrow transplant	40–50%

LD-RT: Low-dose radiotherapy * or relapse within 12 months

Clinical presentation depends on site of origin, though important features include:

a. Painless lymphadenopathy with *typical India-rubber consistency*, usually in cervical region or detected on chest X-ray (mediastinal nodes).
b. Local pressure symptoms, e.g. hoarseness, dyspnea, dysphagia or superior vena caval compression syndrome in mediastinal disease, and
c. Systemic features, e.g. prolonged fever, night sweats, weight loss are prominent in HL, probably due to raised cytokines levels, e.g. interleukins and tumor necrosis factor. Presence of any of these features alters stage of the disease **(Table 20.8)**. *Pel-Ebstein fever* — a relapsing fever, although pathognomonic is seen in only 10–15% cases.
d. Opportunistic infections, e.g. tuberculosis, herpes zoster and fungal infections are common, due to impaired cell mediated immunity.

Diagnosis depends on *excision biopsy* of the suspected lymph node, rather than FNAC, to ensure adequate tissue for histology and immunocytochemistry. Once the diagnosis is established, further investigations are necessary to stage the disease **(Table 20.8)**, which include—(i) bone marrow examination, (ii) chest X-ray/CT for mediastinal or pulmonary disease, (iii) abdominal CT for liver, spleen or node involvement, and (iv) PET scan to stage the disease and assess the response to therapy. ESR, serum LDH and ferritin levels may be monitored serially to assess the effect of treatment.

Treatment depends on the stage of disease and age of patient includes multi-drug chemotherapy with low-dose involved-field radiotherapy **(Table 20.9)**.

Chemotherapy: Most commonly used protocols are preferred *ABVD regimen* (***A***driamycin, ***D***oxorubicin, ***B***leomycin, ***V***inblastine, and ***D***acarbazine) or *COPP regimen* (Cyclophosphamide, ***O***ncovin, i.e. vincristine, ***P***rocarbazine, and Prednisolone), given for minimum 6 cycles. However, considering toxicities of these regimens, e.g. sterility, cardiopulmonary dysfunction and secondary malignancies, many other regimens have been developed to reduce the doses and duration of therapy.

Trials have shown encouraging results with Rituximab-an anti-CD20 antibody, in relapsed cases. EBV-specific cytotoxic T-lymphocytes have also been developed with promising results.

Radiotherapy is highly effective, but with significant adverse effects, e.g. growth failure, cardiac, pulmonary or thyroid dysfunctions and secondary cancers. Several studies have shown that chemotherapy alone is effective in most cases of HL and only limited-field, low-dose (2000–5000 cGy) radiotherapy is used in bulky disease and poor interim PET response to chemotherapy.

Prognosis depends on stage, histological type and systemic features. Important *bad prognostic factors* include—(a) sub-category B disease, (b) bulky mediastinal disease, (c) lymphocytic depletion histology, and d) poor response to chemotherapy. Lymphocyte predominance HL has best outcome.

20.3.2 NON-HODGKIN'S LYMPHOMA

NHL is a heterogeneous group of lymphoid malignancies, which primarily originate from lymphocyte precursors of T, B or indeterminate cells.

Unlike HD, NHL is more common in young children, usually presents as extra-nodal or generalized disease from the outset and carries relatively poorer prognosis, if not treated timely and adequately.

Epidemiology: Incidence of NHL increases with age, with maximum cases between 7 and 10 years. It is more common in males (3:1).

Etiology: While exact etiology is unknown, important associations have been found between NHL and—(a) EBV infection in Burkitt's lymphoma, (b) immunodeficiency states, e.g. AIDS, (c) chronic persistent antigenic stimulation in infections, and (d) chromosomal translocations involving proto-oncogenes or T-cell receptor genes, which regulate their production.

Some pathological subtypes have specific cytogenetic aberrations, e.g. (t8:14) translocation in 90% cases of Burkitt lymphoma.

Pathology: Childhood NHL are divided into 4 major histological types:

a. *Lymphoblastic lymphoma or* LL (30%), from immature T or B lymphocytes,
b. *Burkitt lymphoma or* BL (40%), usually of mature B cell origin,
c. *Diffuse large B cell lymphoma or* DLBCL (20%), with various subtypes, also usually of mature B cell origin,
d. *Anaplastic large cell lymphoma or* ALCL (10%), from mature T or B cells.

Lymphoblastic lymphoma is often indistinguishable from ALL, though presence of >25% blast cells in bone marrow is arbitrarily considered as suggestive of leukemia.

Clinically, Childhood NHL usually presents as extra-nodal disease with rapid growth and distant metastasis to bone marrow and CNS. About two-third of cases have widespread disease at the time of diagnosis. Clinical manifestations depend on the site of tumor and extent of involvement, which in turn depends on histological type.

- *Abdominal mass* is the commonest presentation in NHL, specially in Burkitt lymphoma, with pain, intestinal obstruction, ascites, hepatosplenomegaly and obstructive jaundice.
- *Mediastinal mass* is the second commonest presentation **(Fig. 20.2)**, especially in LL, with airway obstruction, pleural effusion, SVC syndrome and cervical lymphadenopathy.
- Spinal mass may present with severe backache, neurological deficit and raised intracranial pressure.
- Some cases may present with CNS, bone marrow, testis and skin involvement at the time of initial diagnosis.

Diagnosis depends on—(a) lymph node histology with immunophenotyping, (b) assessment for spread of disease by bone-marrow biopsy, CSF examination and imaging studies, e.g. USG abdomen, CT chest, PET scan, etc. *Less than 20% blasts cells on bone marrow virtually rules out leukemia.*

Other important investigations include renal and liver function tests, S. uric acid (to detect tumor lysis syndrome, common in NHL) and S. LDH levels.

St. Jude staging system (Murphy's classification) is commonly used to stage NHL for treatment and prognosis purpose **(Table 20.10)**.

Treatment: Chemotherapy is the mainstay of treatment for childhood NHL, as it is considered a disseminated disease from the time of diagnosis. However, options differ as per histological type.

- ***BL or DLBCL*** are usually treated with 6 cycles of *COMP regimen* (***C***yclophosphamide, ***O***ncovin, i.e. vincristine, ***M***ethotrexate and ***P***rednisolone), over 4–6 months, with >90% cure rate. Addition of Rituximab-an Anti-CD20 monoclonal antibody, is known to improve outcome in adults, and perhaps also in children with NHL. Other regimens, e.g. MCP842, LMB96 are also used in these cases.
- ***Localized or advanced LBL*** required longer-duration chemotherapy for 12–24 months (BFM-90 protocol), similar to that for ALL, including CNS prophylaxis with intrathecal methotrexate or cranial irradiation. Survival rate is 60–80%. Relapses are common and need to be treated more intensively.
- ***Advanced ALCL*** with localized disease may be managed with surgical resection alone, though most cases require chemotherapy with various protocols. Optimum therapy in these cases is controversial with lower cure rate, i.e. 50–70%. CNS prophylaxis with intrathecal methotrexate is also indicated, but cranial irradiation is generally avoided.

Tumor lysis syndrome is very common during initial phase of chemotherapy in NHL due to larger cell mass, which needs to be prevented by appropriate hydration and alkalinization of urine.

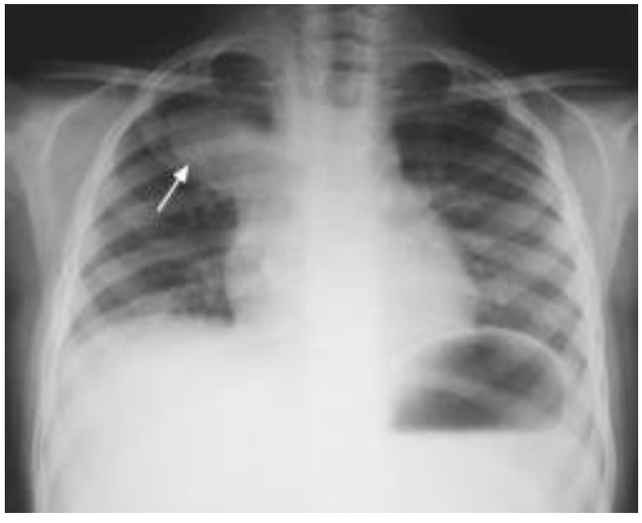

Fig. 20.2: **Mediastinal mass in NHL.**

TABLE 20.10: St. Jude staging system for NHL

Stage I:
- Single extra-nodal or nodal tumor, except of mediastinum or abdomen

Stage II:
- Multiple nodal/extra-nodal tumor, with/out lymphnode involvement, on same side of diaphragm or
- A resectable primary GIT tumor, with/without involvement of mesentric nodes only

Stage III:
- Extra-nodal/nodal tumors on both sides of diaphragm, or
- Primary intra-thoracic tumors, or
- Extensive primary intra-abdominal disease, or
- Para-spinal or epidural tumors

Stage IV:
- Any of the above with CNS/marrow involvement

Surgery has limited role in NHL, except for diagnostic biopsy and intestinal complications, e.g. obstruction, perforation or bleeding.

Radiotherapy is avoided in most cases due to adverse effects, except in mass-effect emergencies, e.g. SVC compression or ureteric obstruction.

Prognosis depends on stage and histological type of disease. *Bad prognostic indicators* include—(i) advanced clinical disease, (ii) CNS or bone marrow involvement at the time of diagnosis, and (iii) large tumor mass. Relapses are more common in non-LBL types, which need to be treated with more intensive chemotherapy or bone marrow transplant.

20.4 NEUROBLASTOMA

Neuroblastoma is the commonest extracranial solid tumor in children, accounting for ~8–10% of all childhood cancers, it is also the commonest tumor in infancy.

Epidemiology: Neuroblastoma is predominantly a tumor of early childhood with peak incidence at 2 years and ~90% cases are diagnosed by 5 years. It may be occasionally present at birth as well.

Family history is present in 1–2% cases, linked to mutations PHOX2B and ALK genes. MYCN amplification, which encodes N-*myc* proto-oncogene proteins, is present in ~15–20% cases, associated with more aggressive disease.

Important associated abnormalities include Neurofibromatosis, Hirschsprung's disease and Beckwith-Wiedemann syndrome. Some parents also have history of occupational chemical exposure.

Pathology: Neuroblastoma originates from *primitive neural crest cells*, which normally develop into sympathetic ganglia and adrenal medulla. Primary tumors usually develop in abdomen (65%) from adrenals or retroperitoneal ganglion, though ~30% arise from cervical, thoracic or pelvic ganglia.

Subsequent course of primary tumors is highly variable, including—(a) spontaneous regression, (b) differentiation into benign ganglioneuroma, or (c) aggressive disease with distant metastasis, more common in older cases.

Common sites of metastasis include bone marrow, lymph nodes, liver and skin. Lung and brain metastasis is rare.

Histologically, it is an encapsulated, small round-cell tumor with three distinct types of prognostic significance: well-differentiated ganglioneuroma, ganglioneuroblastoma and undifferentiated neuroblastoma.

Clinical presentation depends on the site and extent of tumor and includes:

a. Asymptomatic local mass, accidentally palpable in abdomen or visible on chest X-rays.
b. Invasion or compression of surrounding structures with abdominal pain and ascites in abdominal tumors, difficulty in defecation/micturation in pelvic tumors; dyspnea, dysphagia or Horner syndrome in cervicothoracic tumors, and paraplegia or urinary retention in lower spinal tumors.
c. Secondary metastasis with bone pains, pancytopenia, lymphadenopathy, hepatomegaly and bluish skin nodules.
d. Signs of *paraneoplastic syndromes* due to secretion of various substances by tumor, e.g. hypertension (catecholamines), diarrhea (vasoactive intestinal peptides), etc.

Opsoclonus-myoclonus is a rare paraneoplastic syndrome in neuroblastoma due to auto-antibody production against neural tissue, which presents as ataxia, myoclonus and chaotic eye movements (*Dancing eye-Dancing feet syndrome*).

Diagnosis depends on—(a) tissue b*iopsy* for histopathology, cytogenetic studies and molecular markers, along with, (b) *imaging studies*, e.g. CT/MRI to identify extent of primary tumor and metastasis. Urinary catecholamine excretion, e.g. vanillylmandelic acid (VMA) or homovanillic acid (HVA) may be elevated.

Further evaluation is necessary to detect metastasis with—(i) MIBG (meta-iodo-benzyl guanidine) scan to detect silent metastasis, (ii) bone marrow aspirate for neuroblasts, and (iii) PET scan, (iv) molecular studies for N-Myc amplification.

International neuroblastoma staging system (INSS) is commonly used to stage the disease for treatment purpose and asses the outcome **(Table 20.11)**.

Management depends on site of tumor for operational feasibility and stage of disease **(Table 20.11)**.

TABLE 20.11: INSS staging system of neuroblastoma with treatment and survival

Stage	*Extent of disease*	*Treatment survival*	*5-yr*
I	Tumor limited to structure of origin	S	90%
IIa	Local spread but does not cross the midline and LN involvement	S > CT	~85%
IIb	Regional spread but does not cross midline and ipsilateral LN involvement	S > CT+RT	~75%
III	Regional tumor crossing the midline with/without B/L LN involvement	S > CT+RT	~75%
IV	Distant metastasis	CT+RT	15%*
IV-S	Local stage I/II tumor but with disseminated disease (only in infants)	Observe + CT	80%

*beyond 1 year age, better (75%) in infants
B/L: Bilateral; **LN:** Lymphnode
S: Surgery; **CT:** Chemotherapy; **RT:** Radiotherapy

Surgical removal is usually curative in localized disease and indicated for all cases (except stage IV/IV-S tumors very near to vital organs) to confirm histopathology and prevent compressive symptoms. Delayed surgery may be carried out in those with disseminated disease.

Chemotherapy is indicated in all cases except stage I disease, using four drugs — cyclophosphamide, cisplatin, etoposide and vincristine. In advance disease, high-dose chemotherapy followed by bone marrow transplant or use of monoclonal (anti GD-2) antibodies against neuroblastoma cell-surface proteins is under trial.

Radiotherapy is indicated in advanced disease as well as surgically inaccessible tumors or metastasis, e.g. spinal cord compression.

Stage IV-S may regress spontaneously or with low-dose cyclophosphamide/radiotherapy.

Prognosis depends on age (better in infants), staging, histology, and cytogenetic markers (poorer in tumors with chr-1p deletion or amplication of *mycn* proto-oncogene). Relapses are common in cases with high-risk neuroblastoma.

20.5 WILMS TUMOR

Wilms tumor (nephroblastoma) contributes to ~5–6% of childhood malignancies, being one of the commonest solid tumor in under-five children.

Epidemiology: Wilms' tumor is typically a tumor of preschool children with ~75% cases diagnosed by 4 years. Both sexes are equally affected.

Etiologically, while most cases are sporadic, 1–2% of Wilms tumors are familial, more common in younger age with bilateral disease. Genetic mutations have been identified in ~20% cases, specially involving WT1 gene on 11p13.

Wilms tumor is frequently associated with other congenital anomalies, e.g., aniridia, hemihypertrophy or genitourinary malformations; or specific syndromes, e.g., *Beckwith-Wiedemann syndrome* (with macrosomia), *Denys-Drash syndrome* (with genital abnormalities) and *WAGR syndrome* (*W*ilms tumor, *A*niridia, *G*enital abnormalities, mental *R*etardation).

Pathology: Over 90% of Wilms tumors are unilateral, arising as a solitary mass from any part of kidney, leading to distortion of renal outline and compression of residual normal kidney as a thin rim. Wilms' tumor probably originates from incompletely differentiated renal mesenchyme. Histologically, two broad groups are recognized with prognostic significance:

a. *Favorable triphasic histology* with three cell types—epithelial, blastemal, and stromal elements *(90%)*, and
b. *Unfavorable histology* with anaplasia, rhabdoid tumors and clear cell sarcoma *(10%)*.

Tumor may spread locally as an invasive thrombus into renal vein and inferior vena cava (seen in 4–10% cases), or metastasize via lymphatics and blood. Lung is the commonest site of extrarenal metastasis.

Clinically, Wilms tumor presents with a triad of—(a) unilateral abdominal mass, (b) painless hematuria and/or (c) hypertension.

Rare cases present with abdominal pain and vomiting (d/d surgical abdomen), paraneoplastic syndromes, e.g., polycythemia (due to excess erythropoietin secretion) or bleeding diathesis (acquired VonWillebrand like syndrome).

Diagnosis rests on USG, followed by CT-scan to confirm intrarenal origin (*d/d* neuroblastoma), to assess extent of spread and to evaluate functional status of other kidney. Bone scan, neuroimaging and chest X-ray/CT scan is required to detect metastasis.

Immediate total/radical nephrectomy is indicated in all unilateral tumors for staging **(Table 20.12)** and histological classification, along with CT chest and bone scan to exclude metastasis.

Management depends on staging and histological type **(Table 20.13)** of tumor and includes radical nephrectomy in all cases except bilateral tumors, followed by chemotherapy, with/without radiotherapy. Bilateral tumors should receive pre-operative chemotherapy before partial nephrectomy.

TABLE 20.12: National Wilms' tumor staging system

I. Tumor limited to kidney and completely excised
II. Tumor extends through the perineal capsule but is completely excised
III. Residual non-hematogenous tumor confined to the abdomen
IV. Hematogenous metastasis to lung, liver, bone, brain, bone, etc
V. Bilateral renal involvement at diagnosis

TABLE 20.13: Treatment of Wilms' tumor

Stage	*Therapy*	*Survival*
Favorable histology		
I	Sx with/without* 2 drug C	>95%
II	Sx > 2 drug C (18 weeks)	~ 95%
III	Sx > RT + 3 drug C (24 weeks)	~ 90%
IV	Sx > RT + 3 drug C (24 weeks)	~ 85%
V	3-drug C (6–8 week) > Partial nephrectomy	Poor
Unfavorable histology		
All*	Surgery > RT + C3 (15 months)	~ 55%

*Nephrectomy alone may be sufficient in Stage 1 tumors weighing < 550 gm or Age < 2 years.
**Except stage I anaplastic variety, which is treated as those with favourable histology stage I and has good survival (~ 90%).
Sx: Surgery; **C:** Chemotherapy; **RT:** Radiotherapy

For chemotherapy, generally two drugs are used (vincristine + actinomycin), every 1–3 weeks in stage I/II, while a third one-doxorubicin is added in advanced stages or unfavorable histology.

Wilms tumor is highly radiosensitive and postoperative *radiotherapy* is indicated in all cases except stage I and II disease, along with simultaneous irradiation of metastatic lesions in lungs in stage IV disease.

In very large tumors, which are either unresectable or too risky to resect, preoperative chemotherapy followed by delayed surgery is preferred.

Prognosis is generally excellent in appropriately treated cases with 4-year survival of >90%, except in bilateral tumors or unfavorable histology **(Table 20.13)**. Younger age, lower stage and lower tumor weight suggest more favourable outcome, while those with genetic mutations have higher risk of recurrence.

20.6 RETINOBLASTOMA

Retinoblastoma represents 3% of childhood cancers, being the most common intraocular malignancy of childhood.

Epidemiology: Over 95% cases of retinoblastoma occur <5 years of age and ~40% are hereditary, associated with abnormal retinoblastoma suppressor gene (RB1) on chromosome 13q14. Bilateral tumors are almost always hereditary.

Two-hit model suggests involvement of two mutational events in oncogenesis of retinoblastoma – first one being inherited RB1 mutation from parents and second being the acquired mutation in somatic retinal cells. In sporadic retinoblastoma, both mutations occur in somatic cells. Risk of retinoblastoma in the offspring of a parent with RB gene mutation is as high as 97%.

Pathology: Nearly 25% tumors are bilateral. Retinoblastoma usually develops in the posterior portion of the retina, histologically consisting of small, round, blue malignant cells forming rosette. Tumor may spread locally with vitreous seeding or choroidal/optic nerve invasion, followed by distant metastasis.

Clinically, Retinoblastoma presents with leukocoria (cat-eye reflex) with/without diminished vision and strabismus. Advanced disease may present with pupillary irregularity, hyphema, orbital pain due to glaucoma and proptosis.

Diagnosis is confirmed on fundoscopic examination under anesthesia, showing chalky white-grey retinal mass with soft-friable consistency. Orbital CT/MRI is necessary to assess the extent of the tumor, e.g., optic nerve invasion and intracranial extension. Bone marrow aspirate, bone scan and CSF examination may be required in suspected cases to detect extraocular metastasis. *Biopsy of the mass is not indicated.*

Cases with suspected hereditary retinoblastoma should also be screened for RB1 mutations in peripheral blood or tissue samples.

Treatment aims to improve the survival as well as preserve the vision and depends on the size, location and extent of tumor, guided by an international classification.

Various therapeutic modalities includes—(a) focal treatment including transpupillary thermotherapy, cryotherapy and laser photocoagulation, (b) chemotherapy, (c) external beam radiotherapy, and (d) enucleation surgery.

While focal treatment is preferred for intraocular disease, those with large localized lesions may required enucleation. Extraocular extension or distant metastasis may need high-dose chemotherapy, external beam radiotherapy and sometimes, hematopoietic stem cell transplant. Intra-arterial or intra-vitreal chemotherapy has emerged as promising alternatives for refractory disease to preserve the vision.

Genetic counseling is required in all cases of hereditary retinoblastoma. All first-degree relative of a case of hereditary retinoblastoma must be followed up till 7 years of age for development of tumor.

Prognosis in terms of survival is excellent (>90%), though vision may be lost in cases with—(a) large tumors or those located anterior to equator, (b) bilateral disease, and (c) massive orbital or optic nerve involvement. Secondary malignancies, e.g. osteogenic sarcoma, lung and breast cancers are common in hereditary disease.

20.7 SKELETAL MALIGNANCIES

Skeletal tumors are rare in first decade of life with peak incidence in adolescence, commonest being osteosarcoma followed by Ewing's sarcoma. Important similarities and differences between these tumors are given in **Table 20.14**.

Osteosarcoma arise from metaphyseal region of the rapidly growing long bones, e.g. distal femur or proximal tibia. Flat bones are rarely involved.

TABLE 20.14: Osteosarcoma vs Ewing's sarcoma

	Osteosarcoma	***Ewing's sarcoma***
Age	Second decade	
Sex	M > F (1.5:1)	
Metastasis	Lung and bones	
History of injury	Common	Absent
Risk Factors	May be present	Absent
Common site	Long bones	Flat bones
Histology	Spindle cells	Small round cells
X-ray	Sun-ray app.	Onion-peel app.
Treatment	C > surgery	C > RT/Surgery

C: Chemotherapy; **RT:** Radiotherapy.

Histologically, these tumors comprise of highly malignant spindle cells, which produce extracellular osteoid.

Epidemiology: These tumors are most common during physiological growth spurt in adolescents. Important high risk factors include: (a) hereditary retinoblastoma, (b) benign bony lesions, e.g., Paget's disease or Osteogenesis imperfecta, and (c) local radiotherapy for other malignancies. History of minor sport injury is often present. Germline mutations in tumor suppressor genes, e.g., RB1 or p53, are associated with higher risk of osteosarcoma.

Clinically most cases present with non-specific localized signs, e.g. pain, swelling, warmth and restricted movements, frequently misdiagnosed as inflammatory or traumatic lesions in early stages.

Diagnosis depends on biopsy. X-ray may reveal typical *sun-ray or sun-burst appearance* due to osteosclerosis with new bone formation **(Fig. 20.3A)**. MRI is essential to ascertain the extent and operability of primary tumor along with chest CT and PET-scan to detect metastasis.

Treatment includes: (a) preoperative chemotherapy (Doxorubicin, Cisplatin, Ifosfamide and Methotrexate) to shrink the tumor and improve the chances of limb salvage, followed by (b) surgical removal of tumor or amputation, and (c) post-operative chemotherapy.

Outcome: 5-year survival depends on extent of spread, ranging between ~60–70% in non-metastatic and <20% in metastatic disease.

Ewing sarcoma is a member of *Ewing's family*—a group of small round-cell tumors of probably neural crest origin. Other members of this family include neuroblastoma, peripheral primitive neuro-ectodermal tumor (PPNET) and some soft-tissue sarcoma. Chromosomal translocations, e.g. t11:22 are common in Ewing's family of tumors.

Clinically, Ewing sarcoma commonly involves flat bones, e.g. pelvis, spine and chest wall (*Askin tumor*), presenting with local pain, tenderness and swelling. Some tumors may arise from diaphysis of long bones and soft tissues. Systemic manifestations, e.g., fever and weight loss are common.

Diagnosis depends on surgical biopsy. X-rays reveal typical *'onion-peel appearance'* due to aggressive lytic lesions **(Fig. 20.3B)**. Biopsy with immunohistochemistry (CD99, Vimentin) for neural cell markers is necessary to differentiate other round-cell tumors. Metastasis needs to be excluded by bone marrow, chest CT and PET-scan.

Treatment includes preoperative chemotherapy with vincristine, cyclophosphamide, doxorubicin, etoposide and ifosfamide to shrink the tumor, followed by (a) surgical resection, and (b) postoperative chemotherapy.

While Ewing sarcoma is highly radio-sensitive and moderate-dose radiotherapy (5500–6000 cGy) is equally effective, most centers prefer surgical resection for local tumor due to complications of radiotherapy on growing bones. However, radiotherapy is necessary for non-operable tumors.

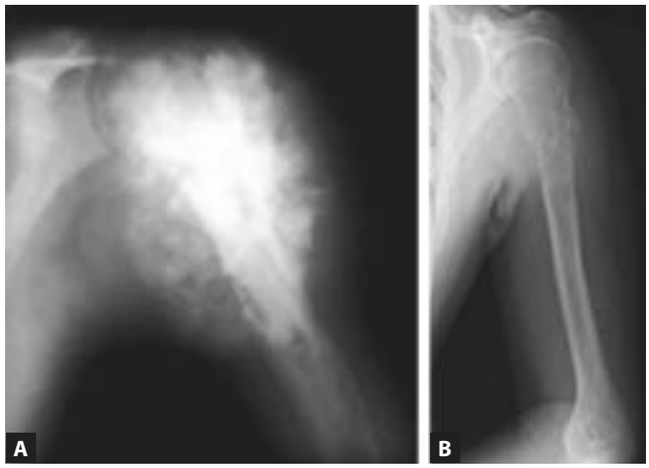

Fig. 20.3A and B: (A) Sun-ray appearance in osteogenic sarcoma; (B) Onion-peel appearance in Ewing's sarcoma.

Prognosis depends on the site and size of primary tumor as well as extent of metastasis, with 5-year survival ranging from 75% in small non-metastatic limb tumors to <20% in pelvic tumors or metastatic disease.

20.8 SOFT TISSUE SARCOMA

Sarcomas account for 6–7% of childhood tumors and include common *rhabdomyosarcoma* and uncommon *non-rhabdomyosarcoma, e.g.* fibrosarcoma, synovial sarcoma, etc.

Rhabdomyosarcoma accounts for ~4% of childhood cancers, more common in males and children with neurofibromatosis.

Pathologically, sarcoma are malignant tumors of primitive mesenchymal tissue and may develop at any site, usually head and neck (25%), genitourinary tract or extremities. Metastasis is common in lung and bones.

Histologically, these are similar to other round cell tumors, e.g. Ewing's sarcoma or neuroblastoma with differentiation based on immunohistochemistry and/or molecular studies.

Three distinct histological types with differences in the treatment and outcome include-*embryonal type* (60%) with intermediate prognosis, *alveolar type* (25–40%) with worst prognosis and *pleomorphic type*, which is rare in childhood (< 1%).

Clinical presentation depends on the site of tumor and compression of neighboring structures. Common presentations include nasal congestion, epistaxis and dysphagia (nasopharyngeal tumors), cranial nerve palsies, headache/vomiting (intracranial tumors) proptosis and diminished vision (orbital tumors) and hematuria, constipation or incontinence (genitourinary

tumors). Vaginal RMS may present as a grapelike mass, coming through vagina (*sarcoma botryoides*).

Diagnosis rests on biopsy with immunochemistry, though CT-scan of the involved part is necessary to delineate tumor mass. Bone marrow studies, chest X-ray/CT and PET scan are also required to detect metastasis. Cystourethrogram is indicated in genitourinary tumors.

Treatment is multidisciplinary, based on location and stage of primary tumor. Completely resectable (Grade I) tumors are treated with surgery and post-operative chemotherapy, while those with regional lymph node involvement or partially resectability (Grade II/III) need surgery followed by chemotherapy as well as local radiotherapy. Grade IV tumors with distant metastasis are inoperable and treated with systemic chemotherapy and irradiation.

Prognosis: 5-year survival varies from ~90% in stage I/II disease, to ~60% in advanced disease. Older children and metastatic disease have poor prognosis.

Non-rhabdomyosarcoma are rare in childhood except fibrosarcoma, which is the commonest soft-tissue sarcoma in infancy.

20.9 HEPATIC TUMORS

Hepatic malignancies in children usually indicate secondary metastasis. Primary liver tumors are rare in this age group, commonest being hepatoblastoma. Second commonest liver cancer, hepatocellular carcinoma is usually seen in adolescents and adults. Uncommon liver tumors include malignant sarcoma or germ cell tumors and benign hamartoma, hemangioma and teratoma.

Hepatoblastoma is an embryonal tumor of hepatic epithelial parenchyma, mostly seen in young children <3 years of age and occasionally associated with other congenital anomalies, e.g. hemihypertrophy, Beckwith-Wiedemann syndrome, diaphragmatic hernia, etc.

Clinically, hepatoblastoma usually present with asymptomatic abdominal mass with/without pain, fever, weight loss and vomiting. Rarely, isosexual precocious puberty or severe osteoporosis with pathologic fractures may be prominent feature due to altered steroid metabolism.

Diagnosis depends on abdominal CT-scan, biopsy and elevated α-fetoprotein levels. X-ray abdomen may reveal intra-tumor calcification in ~30% cases. Chest radiograph/CT is necessary to detect pulmonary metastasis.

Treatment: Complete surgical resection is the only realistic chance of long-term disease free survival in children with hepatoblastoma, though <50% cases have resectable tumors at the time of diagnosis.

However, pre-operative chemotherapy with Cisplatin alone or with Doxorubicin (PLADO) allows resection of initial unresectable tumor in most cases. Pulmonary metastasis needs surgery and chemotherapy.

Prognosis: Three-year survival is >90% in initially resected tumors, ~65% in initially unresectable tumors and ~10–20% in those with metastatic disease.

20.10 HISTIOCYTOSIS

Histiocytosis is a diverse group of rare disorders with excessive proliferation of the cells of monocyte-macrophage system, with infiltration and accumulation of histiocytes within different tissues. Clinical presentation may vary from asymptomatic pathology to severe multisystemic dysfunction.

Histiocytosis is classified into 3 major types **(Table 20.15)**, the commonest in children being *Langerhans cell histiocytosis (LCH).*

Langerhans cell histiocytosis (LCH), is characterized by clonal proliferation of the cells of monocyte lineage, resembling *Langerhans cells*–a normal antigen presenting cell of the skin. Hallmark feature of these cells is presence of CD1a positive *Birbeck granules* (tennis-racket shaped granules in cytoplasm), on electron microscopy.

Clinical presentation depends on the age and extent of disease, as follows:

- *Letterer-Siwe disease,* common in infants with predominantly soft-tissue involvement (multi-systemic disease)
- *Hand-Schüller-Christian disease*, common in toddlers and preschool children, with soft-tissue as well as skeletal involvement, and
- *Eosinophilic granuloma,* common in older children >5 years, with predominantly skeletal involvement.

Clinical features of LCH usually include:

- *Skeletal involvement* (80%) as painless or painful bony swellings, mainly over skull or flat-bones, which appear as osteolytic lesions with sharp punched-out areas on X-rays **(Fig. 20.4)**. Later, these cases may develop pathological fractures, spinal compression or teeth loss due to mandibular involvement.

TABLE 20.15: IHS classification of histiocytic disorders

Dendritic cell disorders
- Langerhans cell histiocytosis
- Secondary dendritic cell processes
- Juvenile xanthogranuloma
- Solitary histiocytoma with dendritic phenotype

Macrophage-related disorders
- Hemophagocytosis syndromes (primary/secondary)
- Rosai-Dorfman syndrome
- Solitary histiocytoma with macrophage phenotype

Malignant histiocyte disorders
- Monocyte related leukemia
- Extramedullary monocytic tumors
- Dendritic cell/ macrophage related histiocytic sarcoma

IHS: International Histiocyte Society

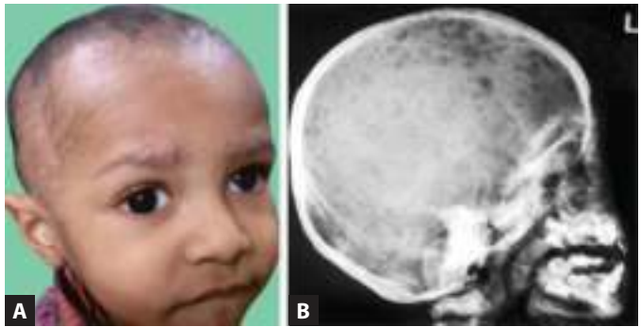

Fig. 20.4A and B: Histiocytosis: (A) Seborrheic dermatitis; (B) Punched out lesions in skull.

- *Skin involvement* (50%) as seborrheic dermatitis **(Fig. 20.4)** or petechial exanthems with/without mucosal involvement, e.g. gingival hypertrophy.
- *Lymphoreticular involvement* with generalized lymphadenopathy and/or hepatosplenomegaly (30%). Signs of chronic hepatic failure may be present.
- *Endocrinal involvement* with growth failure, diabetes insipidus, etc.
- *Bone marrow involvement* with anemia, thrombocytopenia, etc.
- *Uncommon manifestations, e.g.,* chronic lung disease or progressive neurological disease (ataxia, dysarthria), etc. Otitis media is common.

Diagnosis depends on tissue biopsy from suspected skin or bone lesions, to demonstrate CD1a-positive *Langerhans cells with Birbeck granules.* Detailed evaluation is necessary to determine the extent of disease and includes complete hemogram, liver function test, chest and skeletal X-rays for bony lesions, and PET-scan for staging and assessment of response to therapy.

Treatment depends on site and extent of lesions.

Single-system disease (limited to bones, lymph nodes or skin) is generally benign with high chance of spontaneous regression. Treatment in these cases aims to prevent progression of lesion and secondary damage to neighbouring organs, with local curettage, intralesional steroids or low-dose radiotherapy. Skin disease may respond to topical/systemic steroids, topical 20% nitrogen mustard or PUVA therapy.

Multi-system disease (specially involving risk-organs, e.g. liver, spleen, marrow and lungs) needs multi-drug chemotherapy including vinblastine, 6 mercaptopurine and prednisolone, with/without other agents.

Experimental therapies with immunosuppressive agents, e.g. cyclosporine, interferon, or bone marrow transplant is indicated only in unresponsive cases.

Outcome depends on the extent of disease and response to therapy. Late complications include pathological fractures and bony deformities, neurological dysfunctions, chronic pulmonary or liver disease (with exacerbations) and secondary malignancy.

Hemophagocytic lymphohistiocytoses (HLH) are characterized by clonal proliferation of the morphologically normal antigen-processing cells, i.e. macrophages and CD_8 lymphocytes in involved tissues. HLH is attributed to defective functions of natural killer (NK) cells and cytotoxic cells leading to uncontrolled activation of pro-inflammatory cytokines. Many genetic mutations are known for this dysfunction. Two major type of HLH include:

a. *Familial HLH,* an autosomal recessive disorders contributing 25% cases, and
b. *Infection-associated hemophagocytic syndrome,* secondary to viral infections (CMV, EBV, HHV-6), fungi, protozoa and bacteria, often in presence of immunodeficiency.

Rare non-infectious causes of secondary HLH include drugs, e.g. phenytoin, transplant, autoimmune diseases and immunodeficiency states.

Clinically, all forms of HLH present similarly with a generalized disease process – fever, rash (10–60%) and weight loss. Familial HLH usually presents at a younger age (<4 years) than secondary disease. Hepatosplenomegaly, lymphadenopathy and jaundice are common. Neurological involvement usually mimics acute disseminated encephalomyelitis.

Diagnosis rests on the basis of a molecular genetic defect or presence of any 5 of the 8 clinico-pathological criteria **(Table 20.16)**. No absolute distinction can be made between familial and secondary HLH, except on the basis of genetic markers (mutations in performing or Munc13–4 proteins) or positive family history. Acute onset with a documented infection suggests secondary HLH.

Management depends on the probable aetiology.

- ***Familial HLH*** without documented infection, needs multi-drug chemotherapy including Etoposide, Dexamethasone, with/without intrathecal methotrexate. Some recommend antithymocyte globulin and cyclosporine for maintenance phase. Despite initial response, FHLH without transplant is ultimately fatal, due to relapses. Stem-cell transplant is effective in curing ~60% cases.

TABLE 20.16: Diagnostic criteria for hemophagocytic lymphohistiocytoses

- Molecular diagnosis consistent with HLH or
- Any five of the following 8 features
  - Fever (IL-2Rα chain; ≥2,400 U/mL)
  - Splenomegaly (IL-2Rα chain; ≥2,400 U/mL)
  - Pancytopenia Or Bicytopenia (Hb < 9 g/dl or ANC < 1000/μL or PLC < 100000/μL)
  - Hypertriglyceridemia (≥265 mg/dL) or hypofibrinogenemia (≤150 mg/dL)
  - Hemophagocytosis in marrow, spleen or lymph nodes without evidence of malignancy
  - Low/Absent natural killer cell cytotoxicity
  - Hyperferritinemia (≥500 ng/mL)
  - Elevated soluble CD25 (IL-2Rα chain; ≥2,400 U/mL)

- ***Secondary HLH*** needs treatment of underlying infection or other identifiable cause, along with supportive care. Chemotherapy is not required and prognosis is excellent even without specific treatment. However, when a treatable infection or other cause is not documented, chemotherapy is recommended. Intravenous immunoglobulin may be effective in some cases.

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CHAPTER 21

Renal Disorders

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Kidneys are not only the primary excretory organs, but also contribute to many other functions including electrolyte balance, blood pressure regulation, vitamin D metabolism, and secretion of hormones, e.g. erythropoietin and prostaglandins. Apart from primary renal diseases, kidneys are also involved in many systemic disorders or just by being the excretory outlet of body.

21.1 BASIC CONSIDERATIONS

Embryology: Fetal kidneys initially develop in pelvic region from 5th week onwards, before ascending cephalad to lumbar region. Kidneys develop from intermediate mesoderm lying between the paraxial and lateral plate mesoderm on posterior abdominal wall of embryo, via two modes: (a) the collecting system develops from the ureteric bud, i.e. an outgrowth of the Wolffian duct, and (b) renal parenchyma and filtration system develops from the metanephric blastema.

While anatomical nephrogenesis is incomplete till 36 weeks of gestation, urine excretion begins from 10th week onwards, contributing to the amniotic fluid. Presence of oligohydramnios is an important indicator of severe or bilateral renal/urinary tract malformations.

Anatomy: Kidneys are paired, bean-shaped organs, located retroperitoneally in lumbar (L1–4) paravertebral space, right being slightly lower than left kidney. Normal kidney measures ~6 cm and ~24 gm in term newborns and ~12 cm and ~150 gm in adults. Kidneys are relatively protected from trauma due to the location and presence of retroperitoneal fat.

Mature kidneys may be divided into an outer paler layer, i.e. cortex and an inner darker layer, i.e. medulla. Medulla contains 8–12 conical masses pointing towards renal pelvis, i.e. *pyramids*, while cortical tissue that extends between these pyramids forms the columns of Bertini **(Fig. 21.1)**.

Nephrons: Each kidney contains nearly one million nephrons-the functional unit of excretory system. After birth, numbers of nephrons in each kidney remain fixed throughout the life and diseased nephrons are replaced only by scarring, leading to irreversible renal insufficiency.

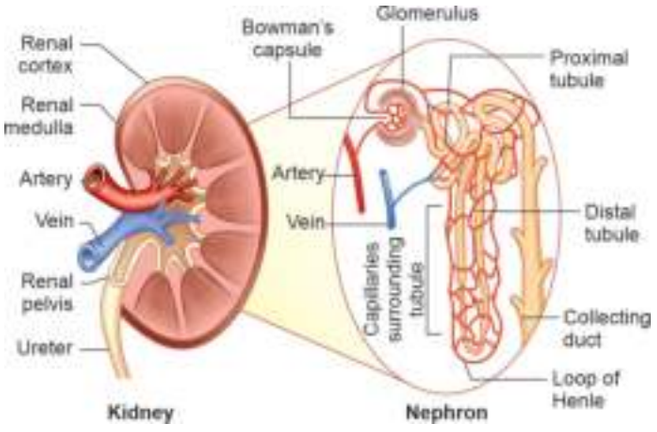

Fig. 21.1: **Renal anatomy.**

Each nephron may be divided into two poles-(a) vascular pole or glomerulus for hemofiltration, and (b) urinary pole or renal tubules for transport of glomerular filtrate to collecting system, simultaneously modifying it by complex processes of reabsorption and secretion of water and electrolytes.

Glomerulus is a highly specialized tuft of capillaries (vascular pole), invaginated into a dilated cup-shaped proximal end of renal tubule, i.e. Bowman's capsule (urinary pole). The space between glomeruli and Bowman's capsule is filled with mesangium-composed of mesangial cells and amorphous matrix, which serves as a supporting structure to capillaries.

Vascular and urinary pole of nephrons are separated from each other by:

- Innermost fenestrated endothelial lining of capillaries that acts as a mechanical filter and does not allow particles of > 110 A° size to pass.
- Glomerular basement membrane (GBM) between capillary endothelium and mesangial cells on inner side and epithelial cells on outer side
- Outer-most visceral epithelial cells of Bowman's capsule with foot processes.

GBM and visceral epithelial layers are in direct continuation with basement membrane and parietal epithelium of Bowman's capsule, respectively.

All these three layers bear a negative electric charge due to presence of a polyionic surface glycoprotein (podocalyxin) and sialic acid, which prevents the filtration of negatively-charged plasma ions, e.g. proteins, by 'same-charge-repulsion'.

Renal tubules are structurally and functionally divisible into proximal convoluted tubules (PCT), loop of Henle, distal convoluted tubules (DCT) and collecting ducts. Collecting ducts ultimately open on a papilla at the apical side of pyramids, to drain the fully formed urine into renal calyces (collecting system)

While glomeruli, PCT, DCT and major portion of collecting ducts are present in renal cortex, the medulla contains ascending and descending arms with loop of Henle, vasa recta and terminal parts of collecting ducts.

Vascular supply is drawn from ipsilateral renal arteries, which sequentially divide into segmental arteries > interlobar arteries > arcuate arteries and > interlobular arteries — the last one feeding afferent arterioles for glomeruli. Efferent arterioles leave from glomeruli and form an extensive network of peritubular capillaries in cortex, essential for tubular reabsorption, secretion and urinary concentration, before emptying into interlobular veins. Some peritubular capillaries that descend into medulla form a loop around the lower end of loop of Henle, i.e. vasa recta. These peritubular networks are essential for tubular reabsorption, secretion and urinary concentration.

Juxtaglomerular apparatus: The ascending part of the distal tubule in medulla that comes in contact with the afferent arteriole of its own glomeruli, contains more dense cells (macula densa). Macula densa, adjoining afferent arterioles and lacis cells located in between, form the juxaglomerular apparatus, which is involved in renin production and electrolyte homeostasis. Renin is a proteolytic enzyme that converts inactive Angiotensin I to active Angiotensin II-a potent vasoconstrictor.

Physiology: Kidneys are primarily involved in: (a) excretion of metabolic wastes and toxic products, (b) regulation of plasma osmolality, electrolytes and acid–base balance, (c) regulation of blood pressure, and (d) other metabolic functions, e.g. renin and erythropoietin production and vitamin D metabolism.

Excretory renal functions may be divided into two components: (a) glomerular filtration, and (b) tubular modification, i.e. reabsorption or secretion.

1. Glomerular filtration mainly depends upon the net result of two opposing forces-capillary hydrostatic pressure (facilitating filtration) and plasma oncotic pressure (opposing filtration), apart from the capillary permeability and glomerular blood flow. Quantitatively, ~20% of glomerular flow is filtered during each passage, with normal glomerular filtration rate (GFR) in adults being ~120 ml/min/1.73 m^2. Qualitatively, nearly all blood components are filtered except cells (due to large size) and high molecular weight proteins (due to large size and negative charge).

2. Tubular modification: This glomerular filtrate is concentrated and modified in composition according to body needs, during its tubular passage to prevent loss of useful substances, e.g. water and electrolytes (tubular reabsorption) and to excrete harmful metabolites (tubular secretion) in urine. Important tubular functions relate to:

- ***Urinary concentration/dilution:*** Freely filtered from glomeruli, ~99% of water in glomerular filtrate is reabsorbed during tubular flow to maintain normal serum osmolality (280–290 mOsm/kg). While ~ 80% of water is absorbed passively in PCT and descending loop of Henle, remaining ~19% is absorbed in collecting ducts under the control of antidiuretic hormone (ADH). Ascending loop of Henle and DCT are impermeable for water. Extent of water reabsorption depends on many factors, e.g. intravascular blood volume and solute load.
- ***Acidification of urine*** is essential to maintain acid-base balance, achieved by reabsorption of filtered bicarbonates (to maintain plasma levels at ~22–24 mEq/L) and secretion of excess H^+ ions (Ch 7.6).
- ***Electrolyte modifications:*** Kidney is major regulator of normal electrolyte balance by increasing or decreasing their urinary excretion, controlled by various hormones and blood levels.
  - *Sodium* reabsorption is closely related to ECF volume. Nearly 99% of filtered Na^+ is reabsorbed actively-65% in PCT (depends upon the amount filtered), 25% in ascending loop of Henle (along with active chloride transport) and rest in DCT and collecting tubules (aldosterone-mediated).
  - *Potassium* is reabsorbed as well as filtered in tubules. Almost all of the filtered potassium is reabsorbed in PCT and whatever is excreted in urine, is actually derived from secretion in DCT and collecting ducts, in exchange to normalize pH and Na^+ concentration of ECF.
  - *Calcium and phosphate* excretions are interlinked and mainly depend on paratharmone levels. About 98% of filtered calcium is reabsorbed, mainly in PCT (65%), facilitated by parathormone. Most of the filtered phosphates are also reabsorbed here, though inhibited by parathormone.
- ***Other substances*** like glucose and amino acids are actively reabsorbed through specific transport systems, usually linked to sodium transport. As these systems have an upper limit for reabsorption/secretion (tubular maxim or Tm), a substance load exceeding its Tm leads to its urinary excretion.

Developmental Immaturities in Newborn

About 95% of newborns void urine within 48 hours of birth. While a newborn has as many nephrons as in an adult, glomerulus is only of 1/3rd size, with short and immature tubules. Some renal functions are not fully mature at birth, rendering them more susceptible for renal failure, electrolyte and acid–base disturbances as well as drug toxicities.

Important developmental handicaps in newborns include:

- *Lower GFR* (20 ml/min/m^2) than in adults (120 ml/min/m^2), rendering them unable to excrete large amount of toxins.
- *Lower urinary concentration capacity* (up to 600 mOsm/kg) than in adults (up to 1200 mOsm/kg), with inability to tolerate excessive fluid loss.
- *Lower urinary acidification capacity* (not <5.5) than in adults, with consequent susceptibility for acidosis.
- *Limited Tm* for glucose, phosphates, bicarbonates, amino acids, drugs and other metabolites, increasing the risk of corresponding abnormalities.

Most of these functions mature by 3–6 months of age. Consideration of these limitations is of paramount importance in young infants during fluid and electrolyte correction as well as drug therapy.

21.2 EVALUATION IN RENAL DISEASE

Etiology of renal disease in childhood varies according to the age. While congenital malformations are commonest renal/urinary tract problems in newborns and infancy, older children usually present with acquired problems, e.g. nephrotic syndrome, acute glomerulonephritis and UTI.

Common clinical indicators of renal/urinary tract disease are:

- Urinary abnormalities, e.g. abnormal color (hematuria, pyuria) or abnormal volume of urine, e.g. (anuria/oliguria or polyuria).
- Micturation abnormalities, e.g. dysuria, frequency, incontinence or secondary enuresis, retention or weak stream of urine, etc.
- Local abnormalities, e.g. lumbar abdominal mass, ureteric colic, etc.
- Systemic abnormalities, e.g. edema, hypertension, growth failure, acidosis, etc. Renal edema is soft and pitting, typically prominent: (a) over face and periorbital region, and (b) during mornings.

Laboratory evaluation in a renal disease depends on probable etiology, though some important and specific investigations in nephrology are discussed here.

Urine examination is considered as the window of renal disease. A freshly voided sample should be used within one hour of collection to avoid misleading results, due to disintegration of formed elements, e.g. cells and bacterial overgrowth. If delay is unavoidable, urine can be stored at 4°C in refrigerator after adding a few drops of acetic acid. Early morning sample is preferred as it is most concentrated and has a lower pH that preserves the formed elements.

Collection of urine sample: Mid-stream clean-catch collection is the most widely used method for this purpose in toilet-trained children. While collections from adhesive urine bags or condom-catheters may be used for biochemical studies, these urine samples are unsuitable for microbial studies due to frequent contamination. Collection of sterile sample in younger children requires either urinary catheterization or suprapubic puncture. Suprapubic puncture is the safe and reliable method to obtain uncontaminated urine sample in infants (Ch 32.6). Important components of urine examination are as follows:

I. Gross examination for:

- ***Quantity:*** A normal child passes ~2–3 ml of urine/kg/hr. Anuria (complete cessation of urine) or Oliguria (<1 ml/kg/hr or 500 ml/1.73 m^2/day) indicates renal failure or obstructive uropathy. Polyuria (>4 ml/kg/hr) may be due to functional polydipsia or pathological, e.g. diabetes insipidus, chronic renal failure and renal tubular acidosis.
- ***Color:*** Urine is normally pale yellow in color, due to presence of urobilin and urochromes. Common color abnormalities include:
  - Dark-yellow, due to concentrated urine, carotenemia, icterus, etc.
  - Red (cola-color) due to: (a) hematuria (b) hemoglobinuria, (c) myoglobinuria, (d) porphyria, or (e) ingestion of drugs, e.g. rifampicin, beet-root of food dyes.
  - Black, in severe hemolysis, e.g. black-water fever, or alkaptonuria
  - Cloudy, due to heavy pyuria or phosphaturia.
- ***Odor:*** Fresh urine has a slightly aromatic odor, which changes to strong ammoniacal smell on standing, due to decomposition of urea into ammonia. A strong fruity-odor indicates presence of ketone bodies.
- ***Reaction:*** Freshly voided urine is acidic (normal pH: 6.0–6.5) due to presence of weak organic acids; but turns alkaline on standing due to formation of ammonia. Alkaline pH of fresh urine indicates UTI due to proteus organisms.
- ***Specific gravity*** (Normal: 1.003–1.030) is tested by floating a urinometer in a glass cylinder, 3/4th full of urine sample. Dependent on the solute-load, urinary specific gravity is decreased in diabetes insipidus and increased in proteinuria, glucosuria or high-solute excretion. In end-stage renal disease, it may be constant at 1.010, due to loss of concentration capacity.

II. Biochemical examination for:

- ***Proteins:*** Normal child does not excrete more than 150 mg of proteins in urine per day, which include low molecular weight tubular proteins, e.g. Tamm-Horsfal proteins (No albumin). Significant proteinuria is defined as the urinary protein excretion exceeding 150 mg/day (>100 mg/m^2/day), which may be qualitatively detected by heat coagulation test, sulphosalicylic acid test or dipsticks or quantitatively by Esbach's method.

  Heat coagulation test: Take ~10 ml of urine in a test tube and heat the upper column. Appearance of turbidity indicates either phosphaturia or albuminuria. Add 2–3 drops of 10% acetic acid. Disappearance of turbidity indicates phosphaturia that persists in proteinuria. Severity of proteinuria may be graded by visibility of printed-paper through turbid solution **(Table 21.1)**.

  Sulfosalicylic acid test: Take ~5 ml of urine and add 5 drops of 10% sulfosalicylic acid. Allow the sample to stand for 5–10 minutes. Turbidity indicates proteinuria, which can be graded as in **Table 21.1**.

  Dipstick method uses special reagent strips, impregnated with tetrabromophenol blue buffered with citrate. When dipped in urine, proteins bind the strip-dye to change its color from yellow to green, which is then compared with color code pasted on the container for semiquantitative values. Proteinuria other than the albuminuria is not detected on dipstick method.

  Note: Heat coagulation, sulfosalicylic or dipstick tests may be false-positive in presence of concentrated or alkaline urine, gross hematuria or drugs, e.g. penicillin; or false-negative in diluted urine sample.

  Esbach's method is used for quantitative estimation of urine proteins. Esbach's albuminometer is filled with urine sample (acidified and diluted to sp. gravity <1.010) till mark 'U', and then topped by Esbach's reagent till mark 'R'. Albuminometer tube is then corked and allowed to stand for proteins to settle down. Height of the precipitate after 24 hours indicates protein excretion in gm/L. 24-hour urinary protein excretion may then be calculated by multiplying this gm/L value with 24-hour urine output.

- ***Glucose (sugar):*** Glucosuria indicates diabetes mellitus or lower renal threshold for glucose excretion (Normal:180 mg/dl), e.g. in renal tubular acidosis. Its presence is generally tested by Benedict test or dipsticks.

TABLE 21.1: Severity of proteinuria

Grade	*Proteins**	*Gross appearance/paper test***
Trace	<30	Slight cloudiness
1+	30–100	Cloudy, but letters identifiable
2+	100–300	Flocculation, only lines identifiable
3+	300–2000	Flocculation, lines not identifiable
4+	>2000	Dense-white precipitate formation

*Approximately in mg/dl
**Place a lined paper behind the tube and look though it.

Benedict test: Add 8 drops of freshly voided urine in 5 ml of Benedict's reagent (alkaline $CuSO_4$ solution). Boil the mixture for 2 minutes to note the color change, if any. Presence of sugar in urine reduces blue $CuSO_4$ into insoluble yellow Cu_2O. Results are graded as-1+ (cloudy) green, 2+ (yellow), 3+ (orange) and 4+ (brick red). Benedict test may be false-positive in presence of other reducing substances, e.g. lactose, fructose, etc. or drugs, e.g. salicylates, vitamin C, etc.

Dipstick uses a cellulose strip impregnated with glucose oxidase, peroxidase and ortho-toluidine. When dipped into glucose positive urine for 30 seconds, color changes to blue due to oxidation of glucose in urine and release of H_2O_2.

- ***Ketones*** (acetoacetate, β-hydroxybutrate) are intermediate products of fat metabolism. Ketonuria is commonly seen in diabetes mellitus or starvation, which may be detected by Rothera's test or Gerhardt test.

  Rothera's test: Saturate 5 ml of urine with ammonium sulfate in a test-tube and add 1 crystal of sodium nitroprusside. When liquor ammonia is added via the side of the tube, a violet color develops at the junction, suggesitve of ketonuria.

  Gerhardt test: Add 10% ferric chloride solution (drop-by-drop) in 5 ml urine, till a precipitate forms. Filter the solution and add more ferric chloride to the filtrate. Development of brownish-red color indicates presence of ketones or salicylates, which may be differentiated by using a boiled sample. Negative test with boiled urine indicates ketonuria, which remains positive in salicylaturia.

- ***Bile pigments*** are present in urine during hepatic disorders and tested by Fouchet test, Foam test or Gmelin test.

  Fouchet test: Add 2.5 ml of $BaCl_2$ in 5 ml of fresh urine and filter. Drip 1–2 drops of Fouchet's reagent over filtered precipitate. A green or blue color indicates presence of bile pigments.

  Foam test: Shake 10 ml of urine in a test-tube vigorously. Development of yellow foam on the top indicates presence of bile pigments.

  Gmelin test: Add equal volume of urine gradually into ½ inch column of yellow nitric acid in a test-tube. Appearance of a green band/ring at the junction indicates presence of bile pigments.

- ***Bile salts*** are also present in liver diseases and tested by Hay's sulfur test.

  Hay's sulfur test: Sprinkle a pinch of sulfur powder over the urine sample in a test tube. Sinking of sulfur particles indicate reduced surface tension of urine due to presence of bile salts.

- ***Blood:*** Presence of hematuria or hemoglobinuria is biochemically detected by Benzidine test or Dipsticks.

  Benzidine test: Mix 2–3 ml of saturated benzidine solution (in glacial acetic acid) with equal volume of urine and add H_2O_2 to mixture. Development of blue color indicates presence of blood.

  Dipstick test: When a reagent-coated cellulose strip is dipped into urine, chromogen is oxidized to give a green-blue color due to pseudoperoxidase activity of hemoglobin.

III. Microscopic examination: 10–15 ml of urine is centrifuged at the rate of 3000 rpm for 5 minutes and

supernatant is poured-off. Concentrated sediment is then examined microscopically for following cellular elements:

- ***RBCs*** appear as small, refractile, non-nucleated bodies. Presence of >5 RBCs/hpf in centrifuged urine or >1–2 RBCs in uncentrifuged sample indicates significant hematuria.
- ***Leukocytes*** appear as bigger and nucleated bodies. Isolated presence of leukocytes is insignificant but presence of >5 WBCs/hpf along with bacteriuria suggests UTI. Most of these leukocytes are polymorphs. Presence of eosinophils in urine on Hansel's staining sample suggests allergic interstitial nephritis. RBCs appear dysmorphic in glomerular lesions.
- ***Epithelial cells*** originate in renal tubules or lower urinary tract and appear as large polygonal and mononuclear cells. Presence of large number of epithelial cells in urine indicates tubular injury.
- ***Bacterial*** contamination is common in wrongly collected or stale urine sample. However, presence of even a single bacteria/hpf in fresh uncentrifuged urine from suprapubic collection indicates significant bacteriuria.
- ***Casts*** are formed in distal tubules and collecting ducts due to coagulation of albuminous material or embedding of degenerated cells in a matrix of tubular (Tamm-Harsfall) proteins. Usually cylindrical in shape, casts may be further classified according to composition as-*RBC casts* in glomerular hematuria, *WBC casts* (pus cells) in upper UTI, *epithelial casts* in tubular disease, *fatty casts* in nephrotic syndrome, *Granular casts* suggestive of disintegrated cells in matrix and *hyaline (waxy) casts*, suggestive of coagulated protein matrix alone without cellular component. Hyaline and granular casts are normally present in urine but increased in fever, after exercise and heavy proteinuria, e.g. nephrotic syndrome.
- ***Crystals,*** suggestive of urolithiasis, are occasionally also present in normal urine and may be made up of-*oxalates* (prism or dumb-bell shaped), *phosphates* (envelope shaped), *uric acid/urates* (orange or reddish spikes), *cystine* (refractile hexagons), etc.

IV. Microbiological studies: A fresh uncontaminated urine sample is essential for microbiological cultures, best obtained by *supra-pubic puncture* or urinary catheterization. However, a clean-catch mid-stream sample is adequate in older children, if collected properly. Presence of any growth from supra-pubic sample is significant, while a colony count of $>10^5$ organisms/ml is considered as diagnostic of UTI on midstream/catheter sample (Ch 21.15).

Renal imaging studies are indicated to identify anatomical renal/urinary tract abnormalities as well as to assess the excretory function.

Plain X-rays of KUB region are of limited value in renal disease, mainly used to detect renal calculi. However, relevant X-rays may be useful to detect co-existing spinal pathology in neurogenic bladder or metastatic bone disease with osteodystrophy or positioning of various catheters and stents.

Intravenous pyelography (IVP) is rarely used now a days to assess renal anatomy and excretory function. After IV injection of an ionic contrast material, e.g. urografin or conray (tri-iodinated benzoic acid compounds), serial films are taken at 1–5 minutes (for renal perfusion), 15 minutes (for renal excretion) and 1–3 hours (for lower urinary tract). IVP is not very useful in newborns due to their inability to concentrate the contrast medium or in chronic kidney disease.

Ultrasonography (USG) is the most widely used imaging investigation in urinary tract disorders to detect—(a) anatomical abnormalities, e.g., congenital anomalies, hydronephrosis, tumors, etc., (b) medical renal diseases, indicated by loss of cortico-medullary differentiation (normally, cortex is less echogenic than medulla), (c) vascular abnormalities by color Doppler studies, and (d) pre-biopsy localization of kidney. Prenatal USG is very useful to detect urinary tract abnormalities in fetus.

Micturating cystourethrogram (MCU) is indicated in a suspected case of vesicoureteric reflux or lower urinary tract abnormalities. It involves introduction of contrast dye into bladder via a catheter or suprapubic puncture, followed by films taken during actual voiding. Oblique and lateral films are needed to detect posterior urethral values.

CT/MRI studies are selectively used to delineate: (a) anatomical abnormalities, (b) mass lesions, e.g. tumors, abscesses or hematomas, and (c) non-functioning kidney.

Radionuclide imaging (renal scan) are rapidly replacing conventional contrast studies, e.g. IVP, in functional evaluation of urinary tract. Common types of renal scans used in practice are:

- ***DTPA*** (^{99m}Tc DTPA) or (^{99m}TcMAG-3) scan for dynamic evaluation of excretory functions, as these agents are rapidly filtered and excreted in urine. This scan is especially useful to detect obstructive urinary tract lesions and renovascular abnormalities.
- ***DMSA*** (^{99m}Tc) scan for static structural evaluation of renal parenchyma, as this agent is sufficiently concentrated in renal tubular cells and very slowly excreted in urine. It is especially useful to diagnose structural abnormalities and cortical scarring.

Renal function tests include tests for assessment of: (a) glomerular filtration (b) renal blood flow, (c) concentration capacity, (d) urinary acidification capability, and (d) other functions.

- **Glomerular filtration** is assessed by direct calculation of GFR or indirectly by rise in blood urea and serum creatinine levels.
  - ***Glomerular filtration rate*** (GFR) is measured by calculating the urinary clearance rate of a substance, which is freely filtered from glomeruli but neither reabsorbed nor secreted from tubules, e.g. inulin< a fructose polymer.

    However in practice, GFR (ml/min/1.73m^2) is usually estimated by *Schwartz formula* using serum creatinine and height values, as follows:

    GFR = K x height in cm/serum creatinine in mg/dl

    Whereas K is 0.33 in infants with birth wt < 2.5 kg, 0.45 in infants, 0.55 in older children and adolescent girls and 0.70 in adolescent boys.

    Normal GFR increases with age from ~20–30/min/1.73 m^2 at birth to ~120 ml/min/1.73 m^2 in adults.
  - ***Blood urea nitrogen*** (BUN) (N: 20–40 mg/dl) is a widely used indicator of glomerular function, though it becomes abnormal only when >75% of renal function is lost. Urea is synthesized in liver from ammonia-an excretory product of protein catabolism.

    Apart from glomerular diseases, BUN may also be increased due to: (a) increased protein absorption after GIT bleeds, (b) excessive endogenous protein breakdown in hypercatabolic states, muscle trauma or steroid therapy, (c) decreased renal blood flow, e.g. dehydration, shock, etc. BUN levels are reduced in low protein intake and severe liver disorders.
  - ***Serum creatinine*** (N: 0.4–0.8 mg/dl): Creatinine is produced endogenously at a near-constant rate by the metabolism of creatine and phosphocreatine in muscles. As its excretion doesn't depend of pre-renal factors (except muscle mass), serum creatinine is a better indicator of GFR than BUN, specially in early renal disease with limited loss of glomerular function. Creatinine levels are also used to adjust drugs dosages in renal failure. Serum creatinine may be falsely low in cases with severe muscle wasting, e.g. malnutrition.
- **Renal blood flow** (N: 500–600 ml/min), although rarely indicated in clinical practice, is measured by assessing the plasma clearance rate of substances, which are completely filtered during the first passage through the kidney, e.g. para-aminohippurate (PAH) or ^{99m}Tc MAG-3.
- **Urinary concentration capacity** is measured as urinary osmolality after standard *water deprivation test*. After overnight water deprivation, a normal child can concentrate the urine >900 mOsm/kg. Inability to concentrate >300–500 mOsm/kg indicates possibility of central or nephrogenic diabetes insipidus, which may be further differentiated by *vasopressin challenge test* (Ch 22.2.4). Substantial improvement in concentration capacity after nasal/IM desmopressin (DDAVP) indicates central diabetes insipidus, while failure to do so indicates nephrogenic disease.
- **Urinary acidification capacity** is impaired in tubular disorders and is assessed by urine acidification tests, e.g. ammonium chloride loading test, i.e. oral administration of NH_4Cl (0.1–0.15 g/kg) to achieve systemic acidosis, followed by pH estimation of all urine samples passed over next 6 hours.

Renal biopsy, being an invasive procedure, is indicated only in select cases with unexplained renal disease, where precise diagnosis is essential for therapy/prognosis.

Indications for renal biopsy generally include: (a) steroid-resistant nephrotic syndrome, (b) progressive renal failure, (c) unexplained persistent hematuria or proteinuria, (d) suspected inherited/metabolic renal disease, (e) follow-up in chronic renal disease or renal transplant.

Procedurally, a ***Vim-Silverman needle with Franklin modification*** or *tru-cut needle* is used for renal biopsy after USG localization of kidney (Ch 32.6). Obtained material should be sent for routine microscopy (in formalin), electron microscopy (in glutaraldehyde) and immuno-fluorescent studies (in saline). A specimen is considered adequate if it contains >10 glomeruli on light microscopy.

Contraindications for renal biopsy include: (a) solitary functioning kidney, (b) ectopic kidney, (c) bleeding diathesis, (d) severe acute renal failure, and (e) severe hypertension.

Complications: While transient hematuria up to 48 hours is inevitable after renal biopsy, significant complications develop in ~10% cases, including: (a) gross/persistent hematuria, (b) perirenal hematoma, and (c) infection. Complete bed rest and BP/output monitoring is essential for first 24 hours after biopsy, to detect complications.

21.3 CONGENITAL RENAL MALFORMATIONS

Congenital or developmental renal malformations are present in 5–10% of children, though most remain asymptomatic and diagnosed incidentally on USG. Congenital abnormalities of kidneys and urinary tract (CAKUT), more common in males, account for ~1/3rd cases of chronic renal failure in children.

Two factors seem to play important role in causation of renal malformations: (a) in utero obstructive uropathy due to associated urinary tract anomalies, (b) inherited defects, e.g. polycystic renal disease.

Classification: Renal malformations may be classified as anomalies of number, ascent, fusion or morphogenesis **(Table 21.2)**.

TABLE 21.2: Important renal malformations

Anomalies of number:
- Unilateral renal agenesis (1:1100)
- Bilateral renal agenesis
- Supernumerary kidney/s

Anomalies of ascent (Ectopic kidney):
- Pelvic kidney (1:1000)
- Thoracic kidney

Anomalies of renal fusion:
- Horseshoe kidney (1:500)
- Crossed renal ectopia

Anomalies of differentiation (Dysplastic kidney):
- Multicystic dysplastic kidney (1:2000)
- Total or sub-total renal dysplasia
- Segmental hypoplasia (Ask-upmark kidney)

Polycystic kidney disease: (hereditary)
- Autosomal recessive (ARPKD)
- Autosomal dominant (ADPKD)

TABLE 21.3: At-birth indicators of renal malformations

- Single umbilical artery
- Oligohydramnios
- Potter facies[1]
- Pulmonary hypoplasia
- Fetal compression syndrome[2]
- Low-set or malformed ears, pre-auricular pits/tags
- Abdominal muscle deficiency *(Prune-belly syndrome)*
- *Urinary tract defect:* Ectopia vesicae, hypospadias.
- Other malformations *(VATER/VACTER association)*[3]

[1]Potter facies, i.e. Low-set ears, parrot-beak nose, receding chin with redundant skin.
[2]Fetal compression syndrome, i.e. Potter facies, pulmonary hypoplasia and deformed limbs, due to renal agenesis > oligohydramnios > fetal compression.
[3]VATER association, i.e. **V**ertebral anomalies, **A**no-rectal malformations, **T**racheo-esophageal fistula, **E**sophageal atresia, **R**enal anomalies and absent head of radius. VACTER association also includes cardiac anomalies.

Diagnosis: Clinical spectrum of renal malformations varies from hydrops fetalis at birth to completely asymptomatic defect, which may remain undetected throughout the life or diagnosed accidentally. Accordingly, diagnosis of these disorders usually depends on:

- ***Antenatal USG,*** revealing abnormal size, location or echotexture of the kidneys, empty bladder and oligohydramnios. *Length of the kidney on prenatal USG in mm approximates the fetal age in weeks.*
- ***At-birth indicators:*** At birth, about 80% of renal malformations are asymptomatic, though the presence of some clinical stigmata **(Table 21.3)** indicates strong possibility of renal disease and need for detailed evaluation. History of oligohydramnios is the strongest indicator of fetal renal disease.
- ***Symptomatic manifestations,*** e.g. abdominal mass, hypertension, oliguria and progressive renal failure.

Some common renal anomalies are as follows:

Renal agenesis, due to failure of development of ureteric bud is mostly unilateral, more common on left side and in males. Unilateral agenesis is usually an incidental diagnosis, but may be associated with other organ malformations or syndromes and need thorough evaluation. Renal functions are well preserved as other kidney takes over the function of absent kidney with some compensatory hypertrophy. These children should avoid contact sports to prevent injury to single kidney. Bilateral agenesis is extremely rare and incompatible with life.

Ectopic pelvic kidneys represent arrested ascent, rotation of fusion of fetal kidneys. These anomalies are also more common on left side (bilateral in 10%) and may remain asymptomatic throughout the life or present with obstructive uropathy and recurrent UTI.

Horseshoe kidney is the commonest renal anomaly, characterized by two renal masses on either side of midline, joined by a functional or fibrotic isthmus at L4–5 level, usually at lower poles (90%). More common in boys and some chromosomal disorders, e.g. Trisomy 18 or Turner syndrome, these patients may be asymptomatic or present with obstructive uropathy in early childhood.

Ask-upmark kidney (Segmental hypoplasia) refers to small kidneys with segmental areas of corticomedullary atrophy, seen externally as transverse grooves. Most cases present in second decade with vesicoureteric reflux, progressive hypertension and renal insufficiency, which needs partial or total nephrectomy.

Congenital hydronephrosis, i.e. dilatation of pelvicalyceal system, is usually a consequence of in utero obstructive uropathy due to urinary tract anomalies.

Mild hydronephrosis (<10 mm pelvic size) is not uncommon on prenatal USG in last trimester due to high urine output, which may resolve spontaneously soon after birth.

As the distinction between transient and progressive hydronephrosis is difficult, all babies with abnormal prenatal USG need follow-up USG at birth, 1 month, 3 months and 6 months. Detailed evaluation with DTPA scan and micturating cystourethrogram is necessary in all cases of abnormal postnatal USGs.

Multicystic dysplastic kidney is the commonest cause of abdominal mass in a newborn, with incidence of ~1:2500–4000 births. Multicystic kidney is usually unilateral, characterized by replacement of normal renal tissue on affected side with multiple cysts of variable size. In utero urinary tract obstruction is considered as a major etiological factor in these cases. Contralateral kidney is usually normal with some compensatory hypertrophy, though 20–40% cases have associated urinary tract lesions.

Being unilateral disease, most cases are asymptomatic in early childhood. Multicystic kidney usually involutes and shrinks by 5–7 years, unless cysts are very large (>6 cm), when surgical removal may be considered. However, periodic follow-up with six-monthly USG is recommended. Risk of malignant transformation or severe hypertension is rare and prophylactic nephrectomy is not indicated.

Polycystic kidney disease is a hereditary disorder with two types—infantile or autosomal recessive (ARPKD) and adult or autosomal dominant (ADPKD).

ARPKD is a rare inherited malformation complex (PKHD1 gene), involving *cystic dilatation of renal collecting ducts and intrahepatic biliary tree*.

Renal manifestations appear in early infancy with enlarged kidneys and progressive renal failure, while hepatic lesions present in late childhood with portal hypertension (congenital hepatic fibrosis). At birth, these children often have oligohydramnios, potter facies, limb abnormalities due to fetal compression and pulmonary hypoplasia with respiratory distress.

Depending on the severity of lesions, these patients die in neonatal period due to pulmonary hypoplasia or survive to develop progressive renal/hepatic disease in later life. Treatment is largely supportive, followed by nephrectomy and renal transplant with/without liver transplantation.

Note that unlike multicystic kidneys, polycystic renal disease is hereditary, bilateral, presents earlier at birth/in infancy and co-existing hepatic cysts are common.

ADPKD is the *commonest inherited renal disease* (PKD1 gene) in adults, though very rarely manifests in childhood. These cases present with abdominal pain or mass, recurrent hematuria, hypertension, nephrolithiasis or chronic renal failure. Liver cysts are usually asymptomatic.

21.4 HEREDITARY NEPHROPATHIES

Hereditary nephropathies include a large number of glomerular and tubulointerstitial disorders **(Table 21.4)** with known inheritance pattern or strong family history. Although rare, these disorders are an important causes of chronic renal failure in young children.

Important hereditary nephropathies may be broadly divided into three categories: (a) renal malformations, e.g. polycystic disease, (b) glomerulopathies, and (c) tubular disorders, discussed in respective chapters. Polycystic kidney disease, nephronophthisis and Alport syndrome are commonest hereditary nephropathies in children.

21.5 HEMATURIA

Hematuria is defined as 'presence of > 5 RBCs/high power field in centrifuged sample *or* >10 RBCs/mm^3 in uncentrifuged urine sample.

TABLE 21.4: Important hereditary nephropathies

Polycystic renal disease

Predominantly glomerular disorders

- Congenital nephrotic syndrome
- Glomerular basement membrane defects
  - Alport syndrome
  - Familial benign hematuria
  - Nail-patella syndrome

Predominantly tubular disorders

- Renal tubular acidosis
- Generalized transport defects
  - Fanconi syndrome
  - Lowe syndrome
- Isolated transport defects
  - Idiopathic hypercalciuria
  - Bartter syndrome
  - Cystinosis
- Urinary concentration defects
  - Nephrogenic diabetes insipidus
  - Nephronophthisis

TABLE 21.5: Causes of hematuria in childhood

Glomerular

- Acute post-infectious GN (APIGN)
  - Acute post-streptococcal GN (APSGN)
  - Other infections
    Bact: Staphylococci, Pneumococci, Salmonella
    Viral: HBV, HCV, CMV, EBV
    Others: Leptospira, malaria, filariasis, candidiasis
    Shunt nephritis, infective endocarditis
- Rapidly progressive GN
- *Chronic GN:* Membranoproliferative GN
- Hemolytic-uremic syndrome
- IgA nephropathy (Berger disease)
- *Vasculitis syndromes:* SLE, HSP
- *Hereditary:* Benign familial hematuria

Extra-glomerular

- *Infections:* UTI, tuberculosis, leptospirosis, HIV
- *Congenital:* Polycystic kidney, A-V malformations
- *Urolithiasis:* Stones, idiopathic hypercalciuria
- *Neoplasms:* Wilms' tumor, bladder tumors
- *Trauma:* Injury, surgery/biopsy, exercise
- *Bleeding disorders:* Purpura, DIC, coagulopathies
- *Vascular:* Renal vein thrombosis, sickle cell disease
- *Drugs:* NSAIDs, cyclophosphamide penicillamine
- *Others:* Acute interstitial nephritis

GN: Glomerulonephritis

Transient asymptomatic microscopic hematuria is not uncommon, seen in 0.5–2.0% of school children and does not require elaborate investigations. However, detailed work-up is required in cases with—(a) gross hematuria, (b) symptomatic hematuria, and (c) persistent microscopic hematuria for >3 months, and (d) recurrent hematuria.

Etiology: Hematuria may be *glomerular* or *extra-glomerular* in origin **(Table 21.5)**. Acute post-streptococcal glomerulonephritis (APSGN) is the commonest cause of glomerular hematuria in childhood, while

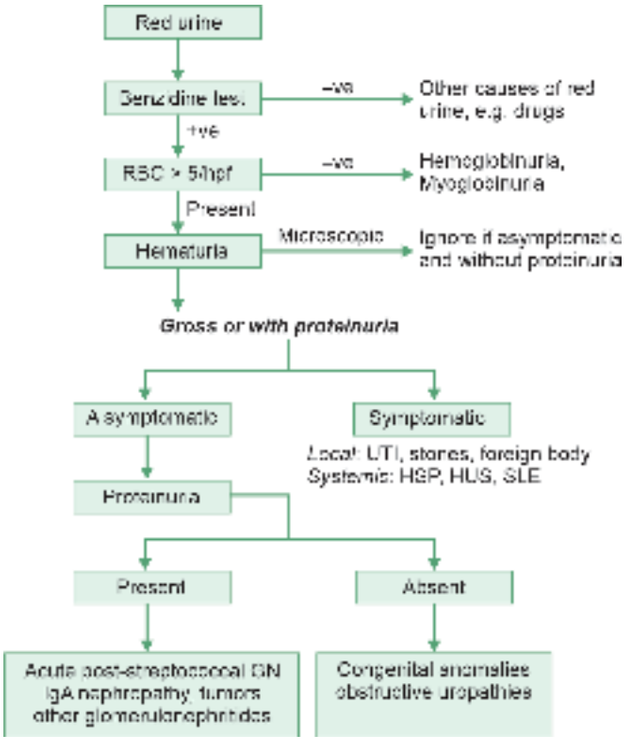

Fig. 21.2: **Diagnostic approach in hematuria.**

extrarglomerular hematuria is usually due to, urinary tract infections, hypercalciuria or stones.

Diagnostic evaluation: An algorithm to evaluate pathological hematuria is given in **Fig. 21.2**, based on following steps:

Step I. To differentiate hematuria from other causes of Red-colored urine, e.g.-(a) hemoglobinuria due to severe intravascular hemolysis, (b) myoglobinuria due to rhabdomyolysis after major trauma or strenuous exercise, (c) porphyria, and (d) drugs, e.g. rifampicin or sugar beet.

A positive *Benzidine test* indicates hematuria, hemoglobinuria or myoglobinuria, excluding other causes of red urine. Presence of fresh RBCs on microscopy generally excludes hemoglobinuria and myoglobinuria.

Step II. To differentiate between glomerular vs non-glomerular hematuria, on the basis of fresh-urine examination, as given in **Table 21.6**.

Step III. Clinical evaluation, based on:

- *Age of presentation:*
  - *Newborn:* Congenital anomalies, bleeding diathesis, renal vein thrombosis, acute cortical necrosis.
  - *Infancy:* Congenital anomalies, Wilms' tumor, Hereditary nephropathies.
  - *Older children:* APSGN, UTI, renal trauma.
- *Past history:*
  - Throat/skin infection in APSGN.
  - *Recurrent hematuria* in IgA nephropathy, benign familial hematuria, Alport syndrome, idiopathic hypercalciuria, etc.
- *Family history:*
  - Congenital anomalies,
  - Hereditary nephropathies.
- *Magnitude of hematuria:*
  - *Gross:* APSGN, IgA nephropathy, Wilms' tumor, bleeding disorders, renal vein thrombosis
  - *Microscopic:* UTI, chronic glomerulonephritis, collagen disorders, urolithiasis.
- *Presence of pain/dysuria:*
  - *Painless:* APSGN, IgA nephropathy, Wilms' tumor, renal tuberculosis, congenital anomalies.
  - *Painful:* UTI, urolithiasis.
- *Co-existing features,* e.g.
  - *Gross edema:* Nephrotic syndrome
  - *Renal mass:* Wilms' tumor, hydronephrosis, etc.
  - *Urinary calculi:* Hypercalcemia, cystinosis, etc.

TABLE 21.6: D/D glomerular *vs* non-glomerular hematuria

Urine examination	*Glomerular*	*Non-glomerular*
Color	Dark brown*	Pink/red
Clots	Absent	Present
RBCs**	Dysmorphic	Normal
RBC casts	Present	Absent
Proteinuria	Common	Absent

* due to acid hematin formation ** On phase contrast microscopy

Step IV. Laboratory evaluation includes:

- *Baseline investigations:*
  - Routine urine examination and culture
  - Radioimaging, e.g. USG
  - *Serology:* ASO titres, Serum C_3 levels
  - *Renal function tests:* BUN, S. Creatinine, Urinary calcium: creatinine ratio
  - *Others:* CBC, X-ray chest, Mantoux test
- *Selective investigations:*
  - Anti-nuclear antibodies (SLE, HSP)
  - Coagulation profile (bleeding disorders)
  - Sickling test (in endemic region)
  - Cystoscopy
- *Renal biopsy* is indicated in all cases of recurrent gross hematuria or persistent microscopic hematuria for >2 years and presence of—(a) significant proteinuria (>1 gm/1.73 m^2/day) or hypertension, (b) persistently low C_3 levels, (c) unexplained kidney failure, (d) family history of significant renal disease.

21.6 GLOMERULONEPHRITIS

Glomeruli are commonest sites of renal pathology, which may be primary or secondary to a systemic disease. Clinically, glomerular disorders present either

as *nephritic syndrome* with predominant hematuria or as *nephrotic syndrome* with predominant proteinuria, though overlapping manifestations are common.

The term *glomerulonephritis* (GN) is generally reserved for glomerular disease of predominantly immunological origin, due to a known or unknown cause. According to the course, glomerulonephritis may be broadly divided into: (a) *acute GN*, (b) *rapidly progressive GN*, and (c) *chronic GN*.

21.6.1 ACUTE GLOMERULONEPHRITIS

Acute glomerulonephritis (acute nephritic syndrome) is a collective term to denote many glomerular disorders (see glomerular causes in **Table 21.5**), all clinically characterized by acute onset of: *(a) hematuria, (b) hypertension, (c) oliguria/anuria, and (d) minimal edema/facial puffiness*.

Over 80% of these cases are preceded by streptococcal infections, termed as *acute post-streptococcal glomerulonephritis* (APSGN), discussed here. However, similar presentation is also seen following many other infections, e.g. staphylococci, pneumococci, etc. and the term "*acute post-infectious glomerulonephritis*" (APIGN) is often used to collectively refer all these cases.

Etiopathogenesis: While over 80 serotypes of group A β-hemolytic streptococci (GABHS) are known, APSGN is a consequence of throat or skin infection with selected nephritogenic strains, commonest being M 49 (causing pyoderma) and M 4 and 12 (causing pharyngitis).

While precise mechanism for glomerular injury in APSGN is unclear, it is most likely an immune-complex disease with either:

- Development of anti-streptococcal antibodies and formation of circulatory immune complexes, which are then trapped in glomerular capillaries, leading to complement activation and consequent glomerular injury; *or*
- Direct subendothelial glomerular injury by GABHS, initiating autoimmune response and *in situ* formation of immune complexes with complement activation, leading to glomerular injury.

Pathologically, characteristic abnormalities are:

- *On light microscopy:* Enlarged glomeruli with—(a) diffuse mesangial and endothelial cell proliferation, (b) obliteration of capillary lumen (blood-less appearance), and (c) increased mesangial matrix with neutrophilic infiltration and crescent formation.
- *On immunofluorescence microscopy:* Lumpy-bumpy deposits of IgG, IgM and C_3 along the capillary walls on glomerular basement membrane and in mesangium (Starry-sky appearance),
- *On electron microscopy:* Subepithelial electron dense hump-like deposits over basement membrane with patchy loss/fusion of epithelial foot processes.

Epidemiology: Preceding history of sore throat or pyoderma is present in >60% cases and epidemiology of APSGN runs parallel to that of streptococcal infections, being more common in: (i) school-age children (5–12 years), (ii) boys, and (iii) certain seasons. APSGN due to pharyngogenic strains is more common in winter, while post-dermatogenic disease is common in summer season.

Latent period between infection and gomerular disease also differs between pharyngogenic (10–14 days) and dermatogenic disease (21 days).

Clinical presentation: A typical case presents with sudden onset of four cardinal features:

1. Gross hematuria with dark cola-colored urine,
2. Mild edema or facial puffiness, more in mornings,
3. Oliguria or anuria, and
4. Hypertension with/without symptoms, e.g. headache and vomiting.

Severe cases may also present with complications, e.g. (a) *hypertensive encephalopathy* with seizures and altered sensorium, (b) *circulatory overload* with pulmonary edema with dyspnoea, and (c) *acute renal failure* with anuria, dyselectrolytemia and acidosis.

Some cases of APSGN present with mixed picture of nephrotic and nephritic syndrome, with marked edema and proteinuria.

Course: Acute phase usually lasts for 2–3 weeks with complete spontaneous recovery in >95% cases, though microscopic hematuria may continue for 3–6 months. Acute renal failure during active phase is common but residual damage or recurrence is very rare.

Diagnosis of APSGN depends on:

- Clinical tetrad of hematuria, hypertension, oliguria and early morning facial puffiness;
- History of preceding sore throat or pyoderma
- Laboratory investigations, e.g.:
  - *Presence of RBCs and RBC casts in urine,* with/without mild proteinuria (< 2+) and pyuria.
  - *Evidence of preceding streptococcal infection,* e.g. elevated ASO titers in ~60% cases. ASO titres may be normal in dermatogenic disease due to interference with antigenicity of streptolysin O by skin lipids. Anti-Dnase B and anti-hyaluronidase titers are elevated in these cases, though rarely used in clinical practice.
  - *Low complement (C_3) level* is a consistent finding (> 90%), suggestive of immune complex injury, which usually normalizes after 6–8 weeks.
  - *Abnormal renal function* tests, e.g. BUN, S. creatinine, S. electrolytes and blood gas analysis, etc.
  - *Renal biopsy* is not routinely indicated except in cases with persistent—(a) gross hematuria, hypertension or azotemia >1 month, (b) persistently low C3 levels for >2 months, and (c) persistent microscopic hematuria or proteinuria for > 12 months.

D/D: APSGN needs to be differentiated from nephrotic syndrome **(Table 21.7)** as well as other causes of hematuria **(Table 21.5)**.

Management: While APSGN is a self-limiting disease; hospitalization is necessary during first week of illness to ensure early recognition and prompt management of complications. Important principles of management include:

- *Systemic antibiotic therapy* with oral penicillin for 7–10 days to control streptococcal infections, if present. However, antimicrobial therapy does not alter the course of APSGN.
- *Regular monitoring* of fluid intake/output, BP, weight and urinary findings, for early diagnosis of fluid retention and hypertension.
- *Salt and water restriction*, only if circulatory congestion, azotemia or hypertension is present.
- *Treatment of volume overload* or pulmonary edema, with fluid restriction and diuretics, if necessary.
- *Treatment of hypertension* with diuretics and antihypertensive drugs, e.g. enalapril. Hypertensive encephalopathy is an emergency that needs IV antihypertensives (Ch 17.12).
- *Treatment of acute renal failure*, if established, as discussed in Ch 21.9.

21.6.2 RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Rapid progressive glomerulonephritis (RPGN) or crescenteric GN is a severe glomerular inflammatory disease of heterogeneous etiology, characterized by rapid deterioration in renal functions within days or weeks and extensive crescent formation on renal histology.

Etiologically, RPGN may be idiopathic or superimposed on other glomerular disorders, e.g. (a) APSGN/APIGN, (b) connective tissue disorders, e.g. SLE or HSP, (c) infections, e.g. shunt nephritis, or (d) goodpasture syndrome.

TABLE 21.7: D/D AcPSGN vs nephrotic syndrome

	AcPSGN	*Nephrotic syndrome*
Age	5–12 years	2–8 years
Past history	Throat/skin infection	Similar attacks
Onset	Acute	Gradual
Edema	+/–	+++
Hematuria	Gross	Rare (<10%)
Hypertension	Common	Rare (<10%)
Azotemia	Common	Rare
Proteinuria	Mild (< 2+)	Severe (3/4 +)
Microscopy	RBCs/casts	N/Fatty casts
Complement	↓	Normal
S. Proteins	Normal	↓
S. Cholesterol	Normal	↑
Histology	Immune deposits	Minimal change
Recurrence	Very rare	Common

Pathologically, it is characterized by widespread crescent formation in majority of glomeruli, due to proliferation of cirumferential layer of fibroblasts, macrophages and epithelial cells within Bowman's space.

Histologically, RPGN may also be classified as: (a) immune-complex GN, (b) pauci-immune GN, and (c) anti-GBM GN.

Clinically, these cases initially present as nephritic or nephrotic syndrome, but progress rapidly to acute renal failure and end-stage renal disease (ESRD). RPGN should be suspected in any case of hematuria, which fails to resolve within 2–3 weeks. Extra-renal manifestations of causative disease, e.g. connective tissues disorders, vasculitis syndromes and infections may be present.

Diagnosis rests on renal biopsy, which is indicated in all cases with severe nephritis which does not resolve in 1–2 weeks.

Management include:

- ***Supportive therapy*** for complications, e.g. uremia, hypertension and hyperkalemia, as well as
- ***Specific immunosuppressive therapy***. Currently recommended schedule include:
  - *Induction phase* with (a) IV Methylprednisolone 15–20 mg/kg/d for 6 days followed by PO Prednisolone 2 mg/kg/day (tapered to 0.5–1.0 mg/kg/day after 4 weeks), and (b) IV Cyclophosphamide 500–750 mg/m^2/dose every 3–4 weeks or PO cyclophosphamide 2 mg/kg/day, for 8 weeks.
  - Subsequent *maintenance therapy* with PO Prednisolone 0.5–1.0 mg/kg/alternate day and PO Mycophenolate 800–1200 mg/m^2/day for next 12–24 months.
- ***Plasmapheresis*** is recommended in cases with anti-GBM GN or dialysis-dependent pauci-immune GN. Rituximab is another potential option under investigation.

Prognosis depends on underlying etiology, severity of disease and timing to start treatment. While some cases recover spontaneously, overall prognosis is poor in those with extensive crescent formation in >80% glomeruli.

21.6.3 CHRONIC GLOMERULONEPHRITIS

Chronic glomerulonephritis is a heterogeneous group of many glomerular disorders, either primary or secondary, with irreversible impairment of renal functions.

While majority of these conditions are idiopathic, chronic glomerulonephritis may be a consequence of renal damage in: (a) hereditary nephropathies, (b) toxic injury following drug/chemical exposure, (c) vascular injury, e.g. in SLE, polyarteritis nodosa, etc., (d) immunological injury, e.g. in viral infections or malaria.

Membranoproliferative GN (MPGN), also termed as *mesangiocapillary GN*, is the commonest cause of chronic

glomerulonephritis in older children and adolescents, presenting as steroid-resistant nephrotic syndrome (60–70%) or persistent hematuria (20–30%).

Diagnosis should be suspected in any case with non-resolving acute nephritis or atypical nephrotic syndrome, and rests on renal biopsy with three histological types:

- *Type I:* Generalized increase in mesangial cells and matrix with immune complex deposits
- *Type II:* Irregular ribbon-like thickening of capillary walls due to dense deposits and crescent formation
- *Type III:* Gross thickening, splitting and layering of glomerular basement membrane.

Long-term alternate day steroid therapy is indicated only in those with heavy proteinuria or impaired renal functions.

Prognosis is poor with gradual progression to ESRD, specially in those with nephrotic presentation.

Membranous nephropathy is the commonest cause of nephrotic syndrome in adults, though rare in children. It is usually seen following infections, autoimmune disorders and drugs, e.g. NSAIDs. Some cases may present with recurrent hematuria.

Pathologically, it is characterized by diffuse thickening of glomerular basement membrane due to immune complex deposits on epithelial side, without significant mesangial proliferation.

Most cases resolve spontaneously though some may continue to have mild/moderate proteinuria. Progression to ESRD is rare.

Other important types of glomerulopathies are as follows:

IgA nephropathy (Berger disease): IgA nephropathy is a common cause of recurrent gross hematuria, pathologically characterized by segmental mesangial proliferation with predominantly IgA deposits in mesangium.

Clinically more common in males, most cases present with recurrent hematuria, often following a bout of mild respiratory infection. Each episode usually lasts for 3–7 days. Proteinuria may appear over time. Diagnosis is based on renal biopsy with immuno-fluorescence studies. Unlike APSGN, C3 levels are normal.

Disease is usually not progressive and treatment is mainly supportive. Cases with mild proteinuria may be treated with ACE inhibitors while immunosuppressive therapy may be required in cases with nephrotic range proteinuria and deteriorating renal function.

Vasculitic nephropathies: Renal involvement with asymptomatic and/or microscopic hematuria and/or proteinuria is common in vasculitis syndromes, e.g. systemic lupus erythematosus (SLE) and Henoch-Scholein purpura (HSP).

Glomerulopathy in HSP (also termed as IgA vasculitis) is usually self-limiting and may be associated with elevated serum IgA levels as well as mesangial proliferation with characteristic IgA deposits in mesangium. Frank nephritis or nephrotic syndrome is rare.

Glomerulopathy in SLE is usually progressive with intermittent course. Renal biopsy may be normal on light microscopy but immunofluorescence studies show IgG and C3 deposits in mesangium and capillary walls. Antinuclear antibodies and low serum C3 are present. Frank nephritic and nephrotic syndrome is common and most cases progress to ESRD after variable period. Steroids with cytotoxic agents may arrest progression of disease.

Hereditary glomerulopathies are rare, but should be considered in differential diagnosis of persistent/recurrent hematuria with similar family history. Three important hereditary nephropathies with predominant glomerular involvement are as follows:

Benign familial hematuria is a rare cause of recurrent gross hematuria with similar family history. Renal biopsy is essentially normal on light and immunofluorescence microscopy but electron microscopy may reveal marked thinning of glomerular basement membrane in some cases. Disease is non-progressive with excellent prognosis.

Alport's syndrome is usually an X-linked disorder, characterized by: (a) renal lesions (diffuse thickening of GBM), (b) sensorineural deafness, and (c) ocular defects, e.g. cataracts, anterior lenticonus and macular lesions. Other organs may also be involved. Most cases present in late childhood with recurrent/persistent hematuria and may progress to end stage renal disease in adulthood.

Idiopathic hypercalciuria, is a common cause of recurrent gross or persistent microscopic hematuria, due to an inherited defect in tubular calcium transport defect, leading to hypercalciuria and recurrent calculi (Ch 21.11).

Goodpasture disease, is characterized by presence of antibodies against type IV collagen present in alveolar basement membrane of the lungs and glomerular basement membrane of the kidneys. Most cases present beyond childhood with recurrent pulmonary hemorrhage and progressive glomerulonephritis. Similar clinical picture is also seen in many vasculitic syndromes, e.g. SLE, HSP, etc., when termed Goodpasture syndrome.

21.6.4 HEMOLYTIC UREMIC SYNDROME

Hemolytic uremic syndrome (HUS) is a leading cause of acute renal failure in young children, characterized by a triad of: *(a) microangiopathic hemolytic anemia, (b) thrombocytopenia, and (c) acute renal insufficiency.* HUS may be broadly divided into two major groups:

- ***Typical HUS*** is associated with Shiga-toxin or shiga-like toxin producing enteropathogens (also termed as Shiga-toxin associated HUS or STEC-HUS), usually seen in infants and toddlers following an episode of diarrhea/dysentery; and

- ***Atypical HUS*** which is less common, seen in older children without antecedent diarrhea/dysentery and associated with genetic abnormalities of alternate complement or thrombotic pathway. However, some attacks may be precipitated by infections, e.g. pneumococci or drugs, e.g. cyclosporine. Secondary HUS following SLE, cancers and marrow transplant is also known.

Etiopathogenesis: Typical HUS in Indian children is usually associated with an attack of bacillary dysentery due to Shiga-toxin producing enteropathogens, e.g. *Shigella dysenteriae 1*, while a Shiga-toxin like verotoxin producing *E. coli* (e.g. *E. coli* O157:H7) is more important cause in Europe and North America.

Cytotoxic injury to endothelium of renal microvasculature due to shiga-like toxins is the primary event in HUS, which provokes activation of platelets and coagulation factors, leading to localized coagulation and fibrin deposition with intravascular trapping of RBCs and platelets (microangiopathy).

Consequently, these cases develop hemolytic anemia, thrombocytopenia and renal ischemia/insufficiency. Unlike DIC, microvascular injury and thrombosis in HUS is relatively localized to renal vasculature, though other organs, e.g. brain may be affected to some extent.

Pathologically, *Thrombotic microangiopathy* is the key finding on renal biopsy in HUS, characterized by:

- narrowing of glomerular capillaries due to swollen endothelium and intraluminal accumulation of blood cells/fibrin thrombi,
- accumulation of foamy fibrillar material in sub-endothelial spaces and mesangium,
- Pre-glomerular arteriolar narrowing with onion-skin appearance due to intimal thickening, and
- Patchy or extensive cortical necrosis.

Clinically, Typical HUS is usually seen in young children below 4 years of age during or within 5–10 days of an attack of acute bacillary diarrhea/dysentery. Onset is characterized by sudden appearance of pallor, oliguria and petechiae/purpura, with/without hematuria and hypertension. Child is extremely irritable and may develop altered sensorium and/or seizures. Many cases rapidly progress to develop acute kidney injury..

Atypical HUS is more common in older children and usually presents with more insidious onset of hematuria, progressive renal insufficiency and severe hypertension. These cases have poorer prognosis with higher risk of developing chronic kidney disease.

Diagnosis rests on typical clinical picture in susceptible age group and combination of three essential laboratory findings, i.e.

1. Hemolytic peripheral smear with distorted erythrocytes, schistocytes, and high reticulocyte count,
2. Thrombocytopenia, and
3. Acute renal failure with elevated BUN and S. creatinine.

Polymorphonuclear leukocytosis, microscopic hematuria and mild proteinuria is common. Interestingly, hypokalemia may be present in early HUS despite renal failure, due to GIT losses of potassium in diarrhea. Renal biopsy is diagnostic, though rarely indicated except in atypical HUS.

Treatment is largely supportive, including management of acute renal failure, hypertension, anemia and concurrent infections. Peritoneal dialysis may be necessary to prevent complications of renal failure. Platelet transfusion should be avoided despite low counts, as transfused platelets are rapidly consumed by the active coagulation and can worsen the disease. *Plasmapheresis* or *Eculizumab* — an anti-C5 antibody that inhibits complement activation, may be beneficial in atypical HUS.

Prognosis: While immediate mortality in adequately treated cases of typical HUS is <10%, 30–40% survivors are left with residual renal damage. Outcome is relatively poor in atypical cases or those with very young age, hypovolemic shock, positive family history, anuria >14 days, severe neurological involvement, gangrenous colitis and severe cortical necrosis on biopsy.

21.6.5 RENAL VEIN THROMBOSIS

Renal vein thrombosis is not a glomerulonephritis (no immunological injury), but discussed here for being an important d/d of gross hematuria and AGN.

Etiology: Renal vein thrombosis is seen with two distinct patterns – in newborns, associated with hypoxia, sepsis, dehydration or infants of diabetic mothers; and in older children, associated with cyanotic CHDs, nephrotic syndrome and inherited hypercoagulable states. Thrombus formation usually begins in intra-renal vessels due to endothelial injury and stasis. Unilateral involvement is more common.

Clinically, renal vein thrombosis usually presents with gross hematuria, flank pain and renal mass. Bilateral involvement may lead to acute kidney injury.

Diagnosis rests on clinical features (hematuria with flank pain/mass), predisposing factors and enlarged hypofunctioning kidney on USG and renal scan. Doppler studies or IVC venography are confirmative, though venographic studies should be avoided due to risk of further vascular damage.

Treatment is largely supportive for unilateral disease with fluid/electrolyte correction and control of infections. Unfractionated or low-molecular weight heparin therapy is indicated in bilateral disease or unilateral disease with IVC extension. Thrombosed kidney may recover gradually or undergo progressive atrophy. Renal scintigraphy is a sensitive screening test to assess evolution of renal dysfunction.

21.7 PROTEINURIA

While large amount of low molecular weight proteins, e.g. globulins and peptide hormones, are filtered through glomeruli, most of them are reabsorbed in proximal tubules. Normal protein excretion in urine does not exceed 100 mg/day or >4 mg/m^2/hour. About half of these are plasma proteins, e.g. albumin and peptide hormones, while rest are derived from distal tubules, e.g. Tamm-Horsfall proteins.

Proteinuria may be detected semi-quantitatively by heat coagulation test, sulphosalicylic acid test or dipstick method; or quantitatively by Esbach's method (Ch 21.2). However, microalbuminuria (15–300 mg/day) precedes appearance of overt proteinuria, which can be detected by sensitive radioimmunoassay.

While 24-hour urinary protein excretion is more reliable indicator of the severity of proteinuria than random tests, it is often difficult to collect proper samples in children. Urinary protein: creatinine ratio (UPCR), with normal value of <0.2 mg/mg after 2 years of age in morning urine sample, correlates well with 24-hour urine proteins and is commonly used to quantify proteinuria in children.

Etiologically, proteinuria may be glomerular or tubular in origin **(Table 21.8)**. Severity of proteinuria often correlates well with underlying pathology and may be divided as follows:

a. Transient mild proteinuria (<300 mg/day or UPCR <0.2 mg/kg)) is common in normal children during fever, stress or after heavy exercise and during non-renal illnesses, e.g. seizures, cardiac failure and does not reflect renal disease.

Orthostatic proteinuria is a benign condition with appearance of mild proteinuria in upright posture only, rarely exceeding 600 mg/m^2/day and characterized by:

- No proteinuria in recumbent posture, i.e. in early morning sample,
- Significant proteinuria (+/++) in standing/ambulatory state, i.e. samples collected after 1–2 hours of morning voiding, and
- Absence of edema or other symptoms.

TABLE 21.8: Causes of proteinuria

- **Mild proteinuria**
  - Orthostatic proteinuria
  - *Transient:* Fever, exercise, drugs*
  - *Non-renal:* Seizures, CCF
- **Tubular proteinuria**
  - Renal tubular acidosis
  - Hereditary tubular nephropathies
  - Acute interstitial nephritis
  - Acute tubular necrosis
- **Acute nephritic syndrome**
- **Nephrotic-range proteinuria**
  - Minimal change nephrotic syndrome (MCNS)
  - Non-MCNS idiopathic nephrotic syndrome
  - Secondary nephrotic syndrome

No treatment is required except follow-up and progression to significant glomerular disease is rare.

b. Tubular proteinuria (<1 gm/1.73 m^2/day or UPCR 0.2–2.0 mg/kg) is characteristically *selective*, i.e. containing low molecular weight plasma proteins with molecular weight less than that of albumin, e.g. peptide hormones or microglobulins. These proteins are normally filtered from glomeruli but reabsorbed in proximal tubules. Tubular proteinuria is seen in proximal tubular disorders, e.g. acute tubular necrosis, interstitial nephritis. renal tubular acidosis or hereditary nephropathies, usually associated with glucosuria, phosphaturia, bicarbonaturia and aminoaciduria. Edema is very rare as there is no albuminuria.

c. Nephrotic range proteinuria (>1 gm/m^2/day or UPCR >2 mg/mg), may be *selective* with loss of plasma proteins having molecular weight less than or equal to that of albumin (minimal change nephrotic syndrome) *or non-selective*, also containing higher molecular weight proteins, e.g. IgG and transferrin. Severe edema is common. Minimal change nephrotic syndrome is the commonest cause of severe proteinuria in childhood.

21.8 NEPHROTIC SYNDROME

Nephrotic syndrome (NS) is a clinical entity related to renal disease, characterized by:

- Heavy proteinuria >1 gm/m^2/day *or* 40 mg/m^2/hr *or* UPCR >2 mg/mg,
- Hypoproteinemia (S. albumin < 3 gm/dl), and
- Presence of edema or generalized anasarca

Over 95% of NS are primary or idiopathic (INS), while the rest are secondary to an identifiable renal or systemic etiology **(Table 21.9)**. This chapter mainly deals with INS, while important causes of secondary nephrotic syndrome are discussed in brief at the end.

Histologically, three main types of lesions are seen in INS, with significant differences in clinical course and response to therapy. Transformation from one to another histological type is uncommon.

TABLE 21.9: Causes of nephrotic syndrome

Idiopathic nephrotic syndrome (INS)
- Minimal change nephrotic syndrome (85%)
- Mesangioproliferative glomerulonephritis (5%)
- Membranous nephropathy (2%)
- Focal segmental glomerulosclerosis (10%)

Secondary nephrotic syndrome
- *Chronic GN:* MPGN, membranous GN
- *Hereditary nephropathies:* Polycystic disease
- *Collagen disorders:* SLE, HSP
- *Tumors:* Leukemia, lymphoma, renal tumors
- *Infections:* HBV, HCV, malaria, HIV, TB, CMV
- *Toxic:* Insect bites, heavy metal poisoning
- *Metabolic:* Diabetes, amyloidosis

Congenital nephrotic syndrome

a. **Minimal-change nephrotic syndrome** (MCNS) is the commonest histological type of NS in children, accounting for ~85% of cases. It is characterized by no significant abnormality on light microscopy and absence of immune-complex deposits on immunofluorescent studies. However, electron microscopy reveals extensive obliteration of epithelial foot processes. Over 95% of these cases respond well to steroid therapy.
b. **Mesangioproliferative nephrotic syndrome** (5%) with diffuse increase in mesangial cells and matrix on light microscopy and presence of immune-complex deposits (IgM and C3) in mesangium on immunofluorescence studies. Severity of mesangial cell proliferation is related to the course of the disease. Only ~50–60% of these cases respond to steroids.
c. **Focal segmental glomerulosclerosis** (10%) with focal sclerotic lesions and scarring, starting from juxtamedullary glomeruli and gradually involving all glomeruli. These cases rarely respond to steroids(<20%) and progress rapidly to end-stage renal disease.

Rare histological types of INS include Membrano-proliferative (MPGN) or membranous nephropathy-latter being the commonest cause of nephrotic syndrome in adults (Ch 21.6.3).

Pathogenesis: Massive proteinuria is the primary pathology in NS, leading to secondary abnormalities, e.g. hypoproteinemia, edema and hyperlipidemia **(Fig. 21.3)**. In MCNS, this proteinuria is characteristically selective, limited to loss of plasma proteins with molecular weight less than that of albumin, sparing larger proteins, e.g. globulins. On the other hand, non-selective proteinuria is common in non-MCNS variants of INS.

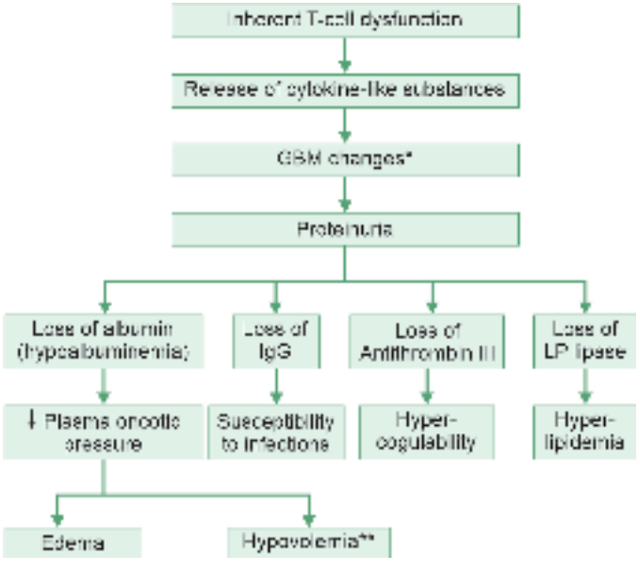

Fig. 21.3: Pathogenesis of nephrotic syndrome
LP: Lipoproteins; **GBM:** Glomerular basement membrane
*Loss of negative charge, pore size, changes in matrix
**Stimulates aldosterone/ADH mediated salt-water retention with further edema

Exact cause of proteinuria in MCNS is unclear. Normally, plasma proteins, e.g. albumin are not filtered in glomeruli due to their size and anionic charge (presence of similar charge on GBM prevents their filtration by same-charge-repulsion phenomenon). Current evidences suggest an underlying immune dysfunction in MCNS, leading to T-cell activation and release of a cytokine-like circulating substance (yet to be isolated), which increases the glomerular permeability for albumin by interfering with the polyanionic endothelial charge or some other unknown mechanisms.

Clinical presentation: MCNS commonly presents between 2 and 8 years of age, more common in males (60–70%). A preceding history of non-specific viral illness is present in some cases.

Edema is the clinical hallmark of NS, which is typically more prominent in periorbital region and during morning hours in early stages. Gradually, it progresses to a stage of generalized anasarca, with marked scrotal and abdominal wall edema. Ascites and pleural effusion may be present in severe cases. Dull abdominal pain and diarrhea is common due to mesenteric and intestinal wall edema **(Fig. 21.4)**.

Oliguria is common in MCNS due to intravascular volume depletion, though other signs of renal disease, e.g. azotemia, hematuria and hypertension are uncommon (<10%) and indicate possibility of non-MCNS pathology.

Diagnosis of NS depends on: (a) characteristic edema, and (b) presence of >2+ proteinuria on repeated testing (>40 mg/m^2/hour or UPCR >2.0 mg/mg) *supported by*, (c) hypoproteinemia, and (d) hyperlipidemia.

Other important investigations include:

- *Urinalysis* for hematuria and hyaline/granular casts
- *Urine culture* to exclude UTI-a common precipitating event for relapses.
- Baseline *Renal function tests*, e.g. BUN, S creatinine and S electrolytes.

Fig. 21.4: Nephrotic syndrome: Facial puffiness, ascites and edema, specially scrotal edema (Inset)
(*Courtesy:* Dr C T Deshmukh)

- *S Complement (C_3) levels*, which are essentially normal in MCNS, but may be reduced in non-MCNS variants or APSGN.
- Investigations to exclude underlying infections, e.g. chest skiagram, TT and HIV/HBV serology, before starting steroid therapy.

Renal biopsy is not routinely indicated except in cases of probable atypical nephritic syndrome (non-MCNS pathology), as indicated by—(a) age of onset < 1 year or > 12 years, (b) gross hematuria or persistent hypertension/azotemia, (c) persistently low C_3/C_4 levels, (d) no response to steroid therapy after 8 weeks, and (e) features of underlying connective tissue disorders, e.g. SLE or IgA vasculitis, chronic infections, e.g. hepatitis B or C and syndromic features, e.g. Nail-Patella syndrome.

D/D of NS includes:

- Other causes of proteinuria/edema — commonest being APSGN **(Table 21.8)**.
- Differentiation between MCNS and non-MCNS disease **(Table 21.10)**.

Course: Over 90% of initial attacks respond well to steroid therapy, though subsequent course is variable and often unpredictable, interrupted by recurrent relapses. Relapses are more likely in younger cases and within first few weeks of remission. Most steroid-responsive MCNS cases stop getting relapses by late adolescence, without residual renal damage. However, steroid-resistant cases with significant renal lesions (non-MCNS) usually progress to ESRF.

Common terms, used to denote course of NS are:

- ***Remission:*** Urine albumin nil or trace (<4 mg/m^2/hr or UPCR <0.2 mg/mg or negative dipstick) for 3 consecutive days;
- ***Relapse:*** Reappearance of proteinuria (>2+ or >40 mg/m^2/hr or UPCR >0.2 mg/mg) for 3 consecutive days, having been in remission previously;
- ***Frequent-relapser:*** Two or more relapses in first 6 months or three or more relapses in any 12 months;
- ***Steroid-dependent:*** Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation;
- ***Steroid-resistant:*** Absence of remission, despite 6 weeks of daily prednisolone (2 mg/kg/day) therapy;
- ***Complicated relapse:*** Relapse with complications requiring hospitalization, e.g.: (a) severe hypovolemia, (b) severe edema, (c) severe infection, e.g. peritonitis, cellulitis or meningitis, or (d) thrombosis;
- ***Significant steroid toxicity*** with hyperglycemia, obesity, short stature, raised intraocular pressure; cataract, myopathy; osteonecrosis or psychosis.
- ***Difficult to treat steroid-sensitive disease*** refers to-(a) frequent relapses or significant steroid toxicity with infrequent relapses, and (b) failure of two or more steroid-sparing agents (including levamisole, cyclophosphamide, mycophenolate mofetil);

TABLE 21.10: D/D MCNS vs. non-MCNS

	MCNS	*Non-MCNS*
Age	2–8 years	> 8 years
Sex	M<F	Equal
Hematuria	<10%	Common
Hypertension	<10%	Common
Azotemia	Rare	Common
*Selectivity**	Yes	No
Serum C_3	Normal	↓
Steroid response	Excellent	Poor
Biopsy	MCNS	Diagnostic

*of proteinuria

Complications are more common during relapses than in initial attack and include:

- ***Infections*** due to edematous skin, impaired phagocytic/opsonin activity and immunosuppressive therapy. Signs of infections and inflammation are often masked in NS, specially in cases on steroid therapy, and diagnosis depends on high risk of suspicion as well as relevant investigations.

  Spontaneous bacterial peritonitis (SBP) is the most important infective complication in NS, which should be suspected in any case with persistent abdominal pain and may need exclusion by abdominocentesis. Other important infections include cellulitis, bone and joint infections, pneumonia, meningitis, UTI, etc.

  Infections due to *capsulated organisms*, e.g. pneumococci, Salmonella and *H. influenzae*, are most common in NS, due to urinary loss of B-factor and consequent impairment in alternate complement pathway. Immunization with influenza, pneumococcal and varicella vaccine is advisable in all nephrotic children.
- ***Thromboembolic complications*** are common due to a hypercoagulable state in NS following hemoconcentration due to hypovolemia, elevated fibrinogen levels, and urinary loss of anticoagulants, e.g. antithrombin III, protein C and protein S. These cases may present with renal vein thrombosis, cerebral strokes or pulmonary embolism.
- ***Hypovolemic shock,*** may develop due to extravascular movement of fluids in hypoproteinemic state, further complicated by diuretics. These cases may develop pre-renal failure with urinary sodium is <10 mEq/L). Intrinsic renal failure is rare in MCNS.
- ***Edema-related complications,*** e.g. skin cracks, sores and infections, are common in NS with severe edema.
- ***Iatrogenic complications*** secondary to long-term steroid therapy, present as steroid facies (moon face with hirsutism), obesity, growth failure, hypertension,

cataracts, glaucoma, hyperglycemia, osteoporosis and avascular necrosis. Immunosuppression may lead to reactivation of tuberculosis and/or severe presentation of common illnesses, e.g. measles and varicella.

Management aims for—(a) control of proteinuria, (b) prevention, early diagnosis and treatment of relapses, and (c) management of complications. Hospitalization is necessary during initial attack for confirmation of diagnosis and in complicated relapses, while uncomplicated relapses may be treated at home. Important steps in management **(Fig. 21.5)** are as follows:

I. Management of first attack involves:

- ***Control of edema:*** Generalized edema is the most important presenting manifestation of initial attack/relapse, which should be managed according to its severity, as follows:
  - No anti-edema measures are necessary in *mild edema* except salt restriction (<2 mEq/kg/d), as steroid therapy itself induces diuresis within one week. Usual amount of salt in diet is permitted but salty snacks or additional intake should be avoided.
  - *Moderate edema* needs some salt-restriction along with diuretics, e.g. PO/IV Furosemide (2 mg/kg/d q8–12hr). Furosemide is a potent diuretic and can cause sudden hypovolemia and electrolyte disturbances, specially Hypokalemia. Simultaneous administration of oral potassium supplements (PO1–2 mEq/kg/day) or a potassium-sparing diuretic, e.g., spironolactone (PO 1–3 mg/kg/day) is advisable.
  - In *severe edema* with marked hypoalbuminemia (Serum Albumin <1 gm/dl), diuretics alone are ineffective and hazardous due to intravascular volume contraction. These cases should receive an IV infusion of human salt-free albumin 5% (0.5–1 gm/kg over 60–90 minutes) to bring back the extravascular fluid in intravascular compartment, before Furosemide therapy.

    Other supportive measures in severe edema include salt and fluid restriction, mechanical measures, e.g. scrotal support to reduce scrotal edema, and abdominocentesis in cases with respiratory embarrassment due to severe ascites.
- ***Exclusion of co-existing infections***, e.g., UTI, tuberculosis, etc. is essential before initiating steroid therapy and requires thorough clinical examination as well as baseline investigations, e.g. urine culture, chest skiagram and tuberculin test in all cases.
- ***Control of proteinuria:*** Immunosuppressive therapy with steroids is the cornerstone of the treatment in INS, irrespective of histopathology. However, it is preferable to delay it for few days after hospitalization to: (a) reduce severe edema as steroids may cause further fluid retention, (b) exclude underlying infection, e.g. UTI or tuberculosis, and (c) wait for spontaneous remission, which is possible in some cases.

  Prednisolone is preferred over other steroids due to relatively less salt/water retention and effect on endogenous cortisol levels. While various regimens are used, *Indian Society of Pediatric Nephrology* (ISPN)

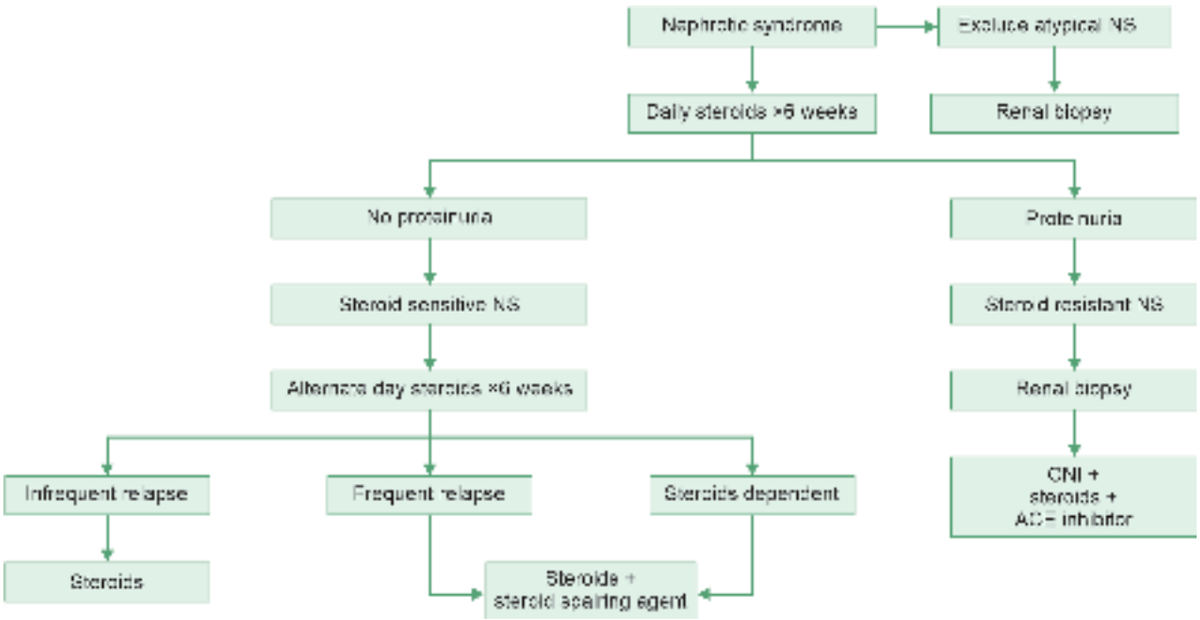

Fig. 21.5: Managemant algorithm for nephrotic syndrome

See text*, **CNI: Calcineurin inhibitors

recommends treatment of the first attack with Prednisolone, as follows:

- PO 60 mg/m^2/day or 2 mg/kg/day (maximum 60 mg) in one/two divided doses for 6 weeks, followed by
- PO 40 mg/m^2/day or 1.5 mg/kg/day (maximum 40 mg) as a single morning dose on alternate days for next 6 weeks.

Single morning dose is preferred in later half of regimen to minimize the effect of exogenous steroids on normal diurnal rhythm in cortisol secretion. Therapy based on body surface area is preferred in young children. After completion of regimen, steroids may be stopped abruptly, without tapering. While most cases achieve remission within 10–14 days, therapy should continue for 12 weeks irrespective of the day of response, to reduce the risk of early relapse.

- ***Regular monitoring*** with daily weight record, intake-output chart and urine examination for proteinuria, till discharge. On discharge, parents must be trained to do daily urine examination for early detection of relapse.
- ***Treatment of complications:***, e.g. infections, thrombo-embolic episodes, hypertension, etc. However, prophylactic antibiotics, antihypertensives or anticoagulants are not recommended.

II. Management of subsequent relapses: Intermittent low-grade proteinuria (>2+) is often triggered by minor infections and disappears spontaneously after control of infections. Persistent proteinuria (>2+) for 3 consecutive days indicates relapse and must be treated on same lines as for first attack but with some differences in duration of prednisolone therapy, as follows:

- PO 60 mg/m^2/day or 2 mg/kg/day in one/two divided doses, until urine protein is trace or nil for 3 consecutive days; followed by
- PO 40 mg/m^2/day or 1.5 mg/kg/day as a single morning dose on alternate days for next 4 weeks.

III. Management of frequent-relapsers or Steroid-dependent cases aims to achieve and maintain remission while minimizing the side-effects of steroids, using long term low-dose steroids along with steroid-dose sparing agents.

After the initial treatment of a relapse as described earlier in "*management of subsequent relapses*", these cases should be treated with:

a. Gradual tapering of the steroid dose to minimum possible, required to keep the patient albumin-free (0.5–0.7 mg/kg alternate days) for 9–12 months;
b. Switch-over of same dose on daily basis (rather than alternate day) for 5–7 days during fever or respiratory infections
c. Addition of a *steroid-sparing agent* in patients failing on alternate-day steroids, steroid toxicity or complicated relapses as follows:

- ***PO Levamisole*** (2–2.5 mg/kg as single dose alternate day) for 1–2 years. Alternate-day steroids may be tapered and discontinued after 3–4 months of starting levamisole. Leukopenia is the main side-effect of Levamisole therapy, which should be monitored every 2 months.
- ***PO Mycophenolate mofetil*** or MMF (PO 600–1200 mg/m^2/day in two divided doses) for 12–36 months along with tapering doses of steroids during initial 3–6 months. Gastrointestinal upset and leukopenia are main side-effects. Therapeutic drug monitoring (TDM) is recommended, if possible. Therapy should be started with lower range of the dose and increased gradually, if TDM is not possible.
- ***PO Cyclophosphamide*** (PO 2–2.5 mg/kg/daily for 8–12 weeks) may induce long-lasting remission in 30–40%, when given along with alternate day Prednisolone (1 mg/kg/day). Hemorrhagic cystitis is common and may be prevented with adequate hydration. Long-term gonadal toxicity and risk of malignancy precludes a second course of treatment.
- ***PO Calcineurin inhibitors,*** e.g. *Cyclosporine* (4–5 mg/kg/day in divided doses) or *Tacrolimus* (0.1–0.2 mg/kg/d in divided doses), are necessary for 12–24 months in cases with difficult-to-treat steroid sensitive NS after failure of 2 of abovementioned steroid-sparing agents. *Renal biopsy is indicated before starting calcineurin inhibitors* and TDM is recommended to adjust the doses for both drugs. Important side-effects of Cyclosporine include hirsutism, hypertension and hyperlipidemia, while tacrolimus leads to hyperglycemia, tremors and seizures. Both drugs are potentially nephrotoxic and renal functions, lipid profile and blood sugar should be monitored every 3 months.
- ***Rituximab***-a monoclonal anti-CD20 antibody (IV 375 mg/m^2 slow infusion) may be used in steroid-dependent NS, who do not respond to other steroid-sparing agents. Considering severe immunosuppression and acute allergic reactions as important side-effects, Patient should be screened for HIV, HBV and HCV prior to the infusion and monitored for acute lung injury or anaphylaxis/serum sickness during or soon after infusion.

IV. Treatment of steroid-resistant NS: Steroid-resistant NS includes those who do not respond during initial attack (primary resistance) or during relapse (secondary resistance). All these cases require:

- *Renal biopsy* before further treatment, which usually reveals FSGS or MPGN histology,
- *Genetic studies* in cases of—(a) congenital NS, (b) primary steroid resistance with onset in infancy, (c) familial steroid-resistance, (d) syndromic NS, and (e) primary steroid-resistance not responding to even calcineurin inhibitors; as many of them have mutations in NPHS2, NPHS1, WT1 and other genes.

- *Screening for secondary causes* of NS, e.g. connective tissue disorders.

While many regimens are used in these cases, therapeutic response is generally unsatisfactory, specially in those with non-MCNS histology or monogenic disease.

Suggested therapeutic modalities, irrespective of histology, include a combination of calcineurin inhibitor (Cyclosporin/Tacrolimus) along with an ACE inhibitor (Enalapril/ Ramipril) and tapering doses of Prednisolone. Patients who respond, usually respond within 3–6 months and even partial response (1+ or 2 + proteinuria or UPCR 0.2–2.0 mg/mg) is acceptable in them.

Patients with monogenic disease are unlikely to respond to immunosuppression and should be maintained on ACE inhibitors and supportive therapy.

ACE inhibitors reduce severity of proteinuria by altering the capillary permeability and reducing glomerular hydrostatic pressure. Side-effects include persistent dry cough or hyperkalemia. Angiotensin receptors blockers, e.g. losartan may be used in cases with persistent cough on ACE inhibitors. Rituximab may be tried in cases after excluding monogenic disease.

Severe hypercholesterolemia may be treated with HMG-coenzyme-A reductase inhibitors.

However, ultimate prognosis is poor in steroid-resistant NS and most cases progress to ESRD in second decade of life. Renal transplant is the last effective option in them, though glomerular lesions tend to recur in transplanted kidney in 15–55% cases.

Other important causes of nephrotic syndrome are as follows:

Congenital nephrotic syndrome is defined as the presence of nephrotic syndrome within 3 months of age. Most of these cases have classic 'Finnish type' disease, though many other conditions are responsible for small number of cases **(Table 21.11)**. Renal biopsy is essential in all cases of congenital NS and response to medical treatment is unsatisfactory, though some patients benefit from renal transplantation.

Finnish-type NS is an autosomal recessive disorder (NPHS 1,2 gene), characterized by typical renal biopsy, i.e. mesangial sclerosis and microcystic dilatation of proximal convoluted tubules. These cases are usually born prematurely with very large placenta and present in neonatal period with progressive edema, failure to thrive, recurrent infections, thromboembolic complications and progression to renal failure within 2–3 years. Elevated alpha-fetoproteins in mother and amniotic fluid suggest possibility of Finnish NS.

Treatment is symptomatic and supportive with periodic IV albumin infusions (every 2–3 weeks), judicious use of diuretics, nutritional supplements and treatment of complications. These cases are steroid-resistant and rapidly progress to ESRD, though ACE inhibitors or Indomethacin may reduce proteinuria in some cases. Bilateral nephrectomy with renal transplant is helpful in many cases.

Secondary nephrotic syndrome is rare in childhood and usually related to inflammatory or coagulatory glomerular insult **(Table 21.9)**. Some important glomerulopathies presenting as nephrotic syndrome have been discussed in Ch 21.6.

TABLE 21.11: Causes of congenital nephrotic syndrome

- Finnish type
- Diffuse mesangial sclerosis
  - Denys-Drash syndrome
  - Galloway-Mowat syndrome
- Primary focal segmental glomerulosclerosis
- *Intrauterine infections:* TORCH, syphilis, HBV

21.9 ACUTE KIDNEY INJURY

Acute kidney injury (AKI), previously termed as acute renal failure (ARF), denotes "rapid deterioration of renal functions, resulting in retention of nitrogenous wastes and complex fluid and biochemical derangements". AKI is considered to be present in cases with:

- Documented oliguria with urine output <0.5 ml/kg/hr for >6 hours, or
- Rise in serum creatinine by >0.3 mg/dl over 8 hours or >50% above the baseline in last 7 days

Severity of the AKI may be further graded into three stages by KDIGO criteria **(Table 21.12)**.

Etiology: Depending on the site of lesion, AKI may be divided into: (a) pre-renal, (b) intrinsic or renal, and (c) post-renal kidney injury **(Table 21.13)**. Diarrhea-induced dehydration and APSGN are the two most common causes of ARF in children.

a. **Pre-renal** AKI (40–55%), is a protective and reversible response to poor renal perfusion, where functional integrity of kidney is well preserved. However, untreated cases may rapidly progress to intrinsic disease.
b. **Intrinsic** AKI (40–50%) involves primary or secondary impairment of glomerular filtration, tubular functions or interstitial damage, leading to complex biochemical abnormalities, which may/may not be reversible.

TABLE 21.12: Staging for acute kidney injury (KDIGO criteria)

Stage	*Rise in S creatinine over baseline*	*Urine output*
1	>150–200% in 7 days, or > 0.3 mg/dl over 48 hr	< 0.5 ml/kg/hr for > 6 hr
2	> 200–300%	< 0.5 ml/kg/hr for > 12 hr
3*	> 300% or >0.5 mg/dl or S creatinine > 4 mg/dl	< 0.3 ml/kg/hr for >24 hr or Anuria > 12 hr

*Or patients on renal replacement therapy or eGFR <35/ml/min/1.73 m^2

TABLE 21.13: Causes of acute kidney injury

Pre-renal causes (impaired perfusion)
- *Fluid loss:* Diarrhea, vomiting
- *Massive blood loss:* Trauma, surgery
- *Hypoproteinemia:* Nephrotic syndrome, burns
- *Hypoperfusion:* Shock, CCF, septicemia

Renal causes (impaired filtration/reabsorption)
- *Glomerulonephritis:* AcPSGN, RPGN, secondary GN
- Hemolytic uremic syndrome
- *Acute tubular necrosis:* Shock, hypoxia, acidosis
- *Infections:* Leptospirosis, septicemia, dengue
- *Drugs:* Aminoglycosides, Amphotericin, NSAIDs
- *Toxins:* Snake bite, hemoglobinuria, heavy metals
- Congenital dysplastic kidney
- *Others:* Hereditary nephropathies, TLS

Post-renal causes (obstructive)
- *Congenital anomalies:* PU valves, PUJ obstruction
- *Functional:* VUR, neurogenic bladder
- *Acquired:* Stones, tumors, blood clot

PU valves: Posterior urethral valves; **PUJ:** Pelvi-ureteric junction; **VUR:** Vesico-ureteric reflux; **TLS:** Tumor Lysis syndrome

c. **Post-renal** AKI (<5%) may be acute or chronic, resulting from obstructive uropathy due to any cause, which lead to increase in intratubular back pressure, medullary damage and consequently, intrinsic renal failure.

Pathogenesis: Irrespective of the etiology, all cases of AKI are characterized by—(a) *volume overload* due to oliguria with Solute and fluid retention, (b) *uremia* due to retention of nitrogenous wastes, (c) *electrolyte abnormalities*, e.g. hyponatremia, hyperkalemia, hyperphosphatemia and acidosis, due to altered tubular functions, and (d) *impairment of non-excretory renal functions*, leading to hypertension (renin-mediated), anemia (erythropoietin-mediated), etc.

Clinical presentation of AKI is generally preceded by features of etiological disease. Important manifestations of established AKI include:
- Oliguria/anuria in >80% cases. Non-oliguric renal failure is common in infants and newborns.
- Edema of variable severity, including pulmonary edema in severe cases.
- Hypertension of variable severity, occasionally leading to encephalopathy, pulmonary edema and retinal hemorrhage.
- Signs of uremia, e.g. vomiting, stress ulcers, bleeding diathesis, encephalopathy, etc.
- Signs of electrolyte disturbances and acidosis
- Signs of primary disease, e.g. hematuria (APSGN), dehydration, pallor, dysentery (HUS), jaundice (Leptospirosis), etc.
- Signs of pre-existing renal disease, e.g. failure to thrive, anemia, rickets, etc.

Diagnostic evaluation: Presence of oliguria/anuria for >6 hours indicates possibility of impending or established AKI, which is confirmed and graded by elevated serum creatinine levels. However, detailed evaluation is essential to identify etiology and exact biochemical status for rational therapy, based on following:

History specially related to preceding events, e.g.
- Frothy or dark urine
- Vomiting/bleeding (pre-renal, HUS)
- Recent Skin/throat infection (APSGN)
- Drug/toxin exposure (interstitial nephritis)
- Fever/jaundice (leptospirosis, malaria)
- Family history (congenital/hereditary renal disease, stones, etc.

Examination specially to detect:
- Dehydration (pre-renal)
- Hypertension (APSGN)
- Palpable kidneys (obstructive uropathy)
- Full bladder (obstructive uropathy)
- Fundus examination (hypertensive changes)

Laboratory investigations
- *Blood examination:*
  - Severe anemia (HUS, chronic renal disease)
  - Hemolytic picture on smear (HUS, renal vein thrombosis)
  - Thrombocytopenia – HUS, vasculitides
- *Urine exam:*
  - Hematuria (nephritis), proteinuria (nephrotic)
  - *Casts:* RBC (Glomerulonephritis), granular or tubular (tubular necrosis)
  - Pus cells (pyelonephritis), eosinophils (interstitial nephritis)
- *Renal functions tests:*
  - BUN, S. creatinine, S. uric acid
  - S. electrolytes and blood gas analysis
- *Immunological studies:*
  - C_3 levels (APSGN, collagen disorders)
  - Antibody titers: ASO (APSGN), ANA (SLE)
- *Microbiological investigations:*
  - Urine culture (UTI)
  - Throat culture (APSGN)
- Others (for complications):
  - Chest X-ray for pulmonary edema
  - Ultrasonography for obstructive uropathy
  - ECG for hyperkalemia

Renal biopsy is indicated only in cases with—(a) rapidly progressive glomerulonephritis, (b) unremitting AKI for >2–3 weeks, (c) unexplained etiology with suspected interstitial nephritis or underling systemic disease, e.g. SLE, IgA vasculitis, etc. However, it should be deferred during anuric phase and in presence of uremia and hypertension.

Presence of *underlying chronic kidney disease* with superimposed AKI should be considered in cases with—(a) growth failure, (b) severe anemia, (c) rickets/mineral bone disease with high PTH, (d) hypertensive retinopathy, (e) contracted kidneys on USG.

Management of AKI aims to: (a) restore renal functions with hemodynamic and biochemical normality, (c) prevent and treat complications, and (d) provide alternative avenues for removal of toxic metabolic products, till recovery of renal functions. A step-wise approach is preferable in most cases, as follows:

Step I. Differentiating between pre-renal and intrinsic AKI: First step in management of AKI is to differentiate pre-renal (hypovolemia) from renal etiology (fluid retention/overload). Simultaneous estimation of urinary and plasma osmolality and sodium concentration is useful to differentiate pre-renal failure from intrinsic disease **(Table 21.14)**. In doubtful cases, a cautious fluid and diuretic challenge strategy may be used to exclude pre-renal failure, as follows:

- ***Fluid challenge:*** In clinically dehydrated cases, IV normal saline (10–15 ml/kg) is given as bolus infusion over 45–60 minutes and urine output is collected preferably by catheterization. Additional boluses may be required in cases with severe dehydration. Urine output of >2 ml/kg in next 2–3 hours indicate probable pre-renal failure and further fluid therapy is continued. However, if oliguria persists, then:
- ***Diuretic challenge:*** In well-hydrated cases or after no response to fluid challenge as above, IV Furosemide (1–1.5 mg/kg) may be administered as a single dose. Urine output of <3 ml/kg in next 3–4 hours suggests intrinsic AKI with stage II/III disease. Furosemide should not be repeated if there is no improvement in urine output, due to potential risk for further AKI and drug-toxicity.

Step II. Management of established/intrinsic AKI: Fluid or diuretic challenge has no role in management of established AKI, who should be managed conservatively, unless indications for dialysis are present, as follows:

- ***Constant monitoring*** for intake, output, weight gain, blood pressure, renal functions (BUN, S.creatinine), and serum electrolytes (Na^+, K^+, Bicarbonates).

TABLE 21.14: D/D pre-renal vs intrinsic renal AKI

	Pre-renal	*Intrinsic*
U. osmolality *(mOsm/kg)*	> 500	< 300
U: P osmolality ratio	> 1.5	< 1.0
U. Na^+ *(mEq/L)*	< 20	> 40
BUN: Creatinine ratio	> 20:1	< 20:1
Fractional Na^+ excretion*	< 1	> 3

*(U. Na^+ × S. creatinine)/(S. Na^+ × U. creatinine) × 100
U: Urine, **P:** Plasma

- ***Fluid restriction:*** Total daily fluid requirement must be restricted to 300–400 ml/m^2/d plus urine output and extra-renal loss in last 24 hours, and given orally or intravenously, as required. Fluid restriction is considered adequate, if patient looses 0.5–1.0% weight per day.
- ***Nutrition:*** As fluid restriction limits the caloric intake, high carbohydrate diet with additional fats is necessary to provide minimum 60–80 cal/kg/day and 1–1.2 gm/kg/day of proteins, along with micronutrient supplements. If oral intake is inadequate, additional calories may be given as concentrated IV infusions.
- ***Correction of dyselectrolytemia,*** which is invariably present in AKI, should be monitored frequently and managed as follows:
  - *Hyperkalemia* is the commonest electrolyte abnormality in AKI. While restricted potassium intake in IV fluids/diet is enough for mild hyperkalemia, severe cases must be treated with IV calcium gluconate, sodium bicarbonate and Dextrose-insulin combination (Ch 7.3). Severe and refractory hyperkalemia is an indication for dialysis.
  - *Hyponatremia* is often dilutional and rarely needs correction unless serum Na^+ levels drop <120 mEq/L or seizures develop, which can be corrected slowly with 3% NaCl solution 6–12 ml/kg over 30–90 minutes. Hypernatremia usually indicates inadequate fluid replacement.
  - *Hypocalcemia* and *hyperphosphatemia* are not as common in AKI as in chronic kidney disease and need to be treated accordingly (Chapter 21.10).
- ***Correction of acidosis:*** Metabolic acidosis is common in AKI due to reduced H^+ and ammonia excretion and needs to corrected with IV $NaHCO_3$ only if serum bicarbonate levels drop <18 mEq/L. Refractory acidosis is an absolute indication for dialysis.
- ***Hypertension*** is usually treated with oral Nifedipine (0.3–3 mg/kg/day q8hr), though severe hypertension or hypertensive crisis may require IV sodium nitroprusside infusion (0.5–8.0 mg/kg/min).
- ***Treatment of other complications*** includes:
  - *Seizures* may develop due to primary cause, hypertension, hyponatremia or uremia, usually treated with IV diazepam (0.2–0.5 mg/kg).
  - *GIT bleeding* may be prevented by antacids and H1 antagonists, e.g. ranitidine. Aluminium-containing antacids should be avoided due to higher risk of aluminium toxicity in uremia.
  - *Anemia* is rarely severe and usually indicates dilution of ECF due to fluid retention. However, severe anemia (Hb >7 gm/dl) needs low-dose packed cell transfusions (3–5 ml/kg) cautiously due to risk of overload or exchange transfusion.
  - *Pulmonary edema* is treated with oxygen supplementation, diuretics and dopamine infusion.

TABLE 21.15: Indications for dialysis

- Severe uremia with fluid overload (Pulm. edema)
- Severe/refractory hyperkalemia *(> 6.5 or ECG signs)*
- Severe/refractory metabolic acidosis *(pH < 7.2)*
- Severe/refractory hypertension, encephalopathy
- Dialyzable poisonings, e.g. *barbiturates, salicylates*
- Severe catabolic states, e.g. sepsis, burns, HUS, etc.
- Inborn errors of metabolism, e.g. *urea cycle defects*

  – *Control of infections:* While prophylactic antibiotics are not recommended, nosocomial infections are common and should be treated with antibiotics in modified doses as per creatinine values.

Step III. Dialysis is indicated in refractory cases to conservative therapy, to remove excess of toxic metabolites **(Table 21.15)**. There are three modalities for dialysis: *(a) peritoneal dialysis, (b) intermittent hemodialysis, or (c) continuous kidney replacement therapies (CKRT).*

While the choice of procedure depends on the age, hemodynamic status, integrity of peritoneal membrane and available facility/expertise, most cases in children can be successfully managed with simple, economical and effective peritoneal dialysis.

Peritoneal dialysis (PD) involves removal of toxic metabolites in the capillary blood by allowing them to equilibrate with dialysis fluid in peritoneal cavity, across the semi-permeable peritoneal membrane. The net trans-membrane movement of solutes is determined by osmotic gradient, electric gradient, molecular weight and pore size.

Indications: PD is preferred mode of dialysis in children with: (a) acute kidney injury, (b) dialyzable poisonings and (c) to tide over the crisis in chronic renal failure, till other modes of renal replacement therapy, discussed later are possible.

Procedure: PD is a simple procedure that involves:

- *Insertion of appropriate size PD catheter,* usually in midline between umbilicus and pubic symphysis, directed towards right iliac fossa;
- *PD cycles,* i.e. infusion of 30–50 ml/kg of commercial PD fluid through PD catheter (inflow), allowing it to remain in peritoneal cavity for some time (30–60 minutes) for diffusion of solutes (dwell-time) and finally, the removal of fluid using siphon-effect through same catheter. Same steps are repeated till biochemical parameters return to safe limits, with each cycle lasting for ~ 60–70 minutes, including 5–10 minutes of inflow time, 30–60 minutes of dwell time and 5–10 minutes of outflow time.

  Usually 30–40 cycles are performed initially, using commercial lactate-based dialysates with 1.36% dextrose, though higher concentrations of 2.5–3% may be used for faster ultrafiltration. Potassium should be added only after first 5–10 cycles as 3 mEq/L.
- *Serial monitoring* of renal parameters, e.g. BUN, creatinine and electrolytes, to modify the speed of infusions, dwell time, composition of PD fluid and to decide about stoppage of PD.

Contraindications for PD include: (a) severe ascites/peritonitis, (b) severe bleeding tendencies, (c) abdominal wall defects or prior abdominal surgery/adhesions. In these cases, hemodialysis is necessary.

Complications of PD include: (a) local trauma, e.g. gut perforation, (b) infections, e.g. peritonitis, (c) metabolic problems, e.g. dyselectrolytemia, hyperglycemia (due to high dextrose PD fluid), (d) abdominal distension with respiratory embarrassment, and (e) procedure-related, e.g. leak/blockage of catheter. Risk of infection is directly related to duration of catheter *in situ*, and PD should not be continued from the same site for >72 hours.

Hemodialysis is the more efficient but more expensive option, which requires adequate infrastructure, expertise and good vascular access. It is also unsuitable for hemodynamically unstable patients or those with bleeding disorders.

HD requires HD machine, pediatric size dialyzers with tubings and Dialysate fluid. A double-lumen long venous catheter is used for vascular access, usually through femoral, internal jugular or subclavian veins, with each cycle lasting for 3–4 hours. Complications include hemodynamic instability, vascular access injuries and dialyzer reactions.

Continuous kidney replacement therapy (CKRT) is an extracorporeal purification technique, used round-the-clock in sick and hemodynamically unstable patients in ICUs, though it is expensive, needs expertise and carries risk of bleeding. Modalities include continuous venovenous hemofiltration or hemodialysis (CVVH/CVVHD), continuous venovenous hemodiafiltration (CVVHDF) or slow continuous ultrafiltration (SCUF).

Some specific situations with AKI are as follows:

AKI in newborns is defined as Oliguria <1ml/kg/hr for 6–12 hours or Serum creatinine rise of > 0.3 mg/dl in 48 hours or >50% rise in 7 days. S. Creatinine >2.5 mg/dl indicates stage III AKI in newborns.

Etiologically, AKI in newborn is secondary to birth asphyxia. Sepsis, hypovolemia, congenital anomalies, nephrotoxic drugs or renal vein thrombosis.

Management is similar to that in older children, though fluids should be limited to 30 ml/kg/day (50–100 ml/kg/day in preterms) and peritoneal dialysis is preferred. However, abdominal distension with respiratory embarrassment should be watch for and dialysis fluids should be carefully warmed to avoid hypothermia.

Acute cortical necrosis is a common cause of AKI in newborns following asphyxia, shock, DIC etc, while in older children it is mostly seen with HUS, burns or snake-bite.

Histopathologically characterized by presence of cortical infarcts in involved portions, most cases present with acute hematuria or renal failure.

Diagnosis is supported by USG (enlarged unobstructed kidneys) in a suspected case, with poor or no renal blood flow or function on renal scan.

Treatment is supportive and prognosis depends on amount of surviving cortex.

TABLE 21.17: Causes of chronic kidney disease

- *Chronic glomerulonephritis:*
  - *Idiopathic:* MPGN, MGN
  - *Secondary:* HSP, SLE, polyarteritis nodosa
- *Hemolytic:* Uremic syndrome
- *Congenital anomalies:* Polycystic or dysplastic kidney
- *Hereditary:* Alport syndrome, nephronophthisis
- *Obst. uropathy:* PUJ obstruction, PU valves, VUR
- *Others:* Amyloidosis, Wilms' tumor, cortical necrosis

21.10 CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is defined as—*(a) abnormalities of kidney structure or function for >3 months, with or without decreased GFR; or (b) GFR < 60 ml/min/1.73 m² for >3 months without any structural or functional renal damage.*

End-stage renal disease (ESRD) is the terminal phase of CKD, when life cannot be sustained without renal replacement therapy, e.g. dialysis or transplantation.

Severity of CKD is usually classified on the basis of GFR as per NKF-KDOQI classification **(Table 21.16)** or KDIGO classification. KDIGO classification also stage CKD in 5 grades (G1–5) similar to NKF classification, except sub-classifying Stage 3 into G3a (GFR 45–59) and G3b (GFR 30–44).

Etiology of CKD varies with age. While developmental renal anomalies and obstructive uropathies are common in under-five children, acquired lesions, e.g. glomerulonephritis, hemolytic uremic syndrome and hereditary nephropathies dominate in older children **(Table 21.17)**.

Pathogenesis: Kidney has a remarkable reserve to maintain its functions despite the loss of large number of nephrons, by compensatory hyperperfusion and hyperfiltration in remaining nephrons. However, such diversionary mechanisms further add to renal insult, probably by increasing hydrostatic pressure in surviving glomeruli, leading to proteinuria and progressive glomerular sclerosis (hyperfiltration injury).

TABLE 21.16: Staging of chronic kidney disease. (NKF-KDOQI Guidelines*)

Stage	*Description*	*GFR**
1	Kidney damage with normal/increased GFR	>90
2	Kidney damage with mild decrease in GFR	60–89
3	Moderate decrease in GFR	30–59
4	Severe decrease in GFR	15–29
5	Kidney failure, dialysis dependence	<15

*in ml/min/1.73 m²
NKF-KDOQI: National kidney foundation – Kidney disease outcomes quality initiative

Once a critical mass of nephrons in lost, either due to primary disease or hyperfiltration injury, progressive decrease in GFR ultimately lead to increasing severity of CKD and finally reaching to ESRD **(Fig. 21.6).** Proteinuria, hypertension and metabolic disturbances, e.g. hyperphosphatemia also contribute to progression of CKD.

Terms chronic renal insufficiency, CKD and ESRD, are also used to signify GFR reduction, below 50%, 25% and 5% respectively.

Clinical manifestations of CKD appear insidiously with:

- *Growth retardation* due to poor nutrition, metabolic acidosis, anemia and reduced responsiveness to growth hormone. Puberty and skeletal growth is also delayed, with ultimate short stature.
- *Edema* due to fluid and salt retention.
- *Hypertension* due to renin-angiotensin mechanism and fluid retention.
- *Normocytic normochromic anemia* due to reduced erythropoietin production, uremic suppression of bone marrow and decreased RBC life span.
- *Bleeding tendencies,* e.g. GIT bleeding, due to thrombocytopenia (bone marrow depression) and defective platelet functions.

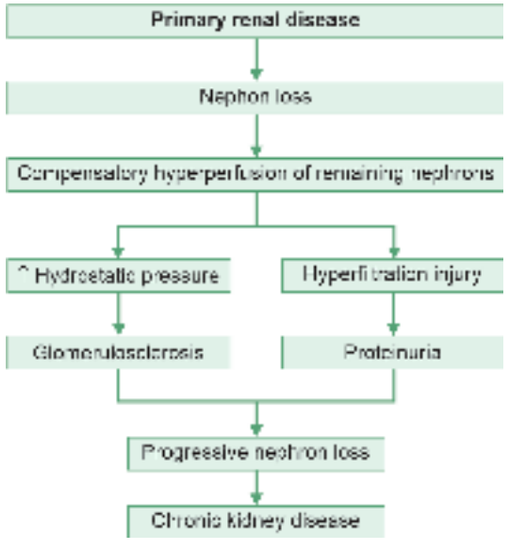

Fig. 21.6: Pathogenesis of chronic kidney disease.

- *Renal osteodystrophy*-a spectrum of bone diseases due to hyperphosphatemia (↓ excretion), hypocalcemia (secondary to hyperphosphatemia), compensatory hyperparathyroidism and vitamin D {1, 25 $(OH)_2$ D3} deficiency. These cases present with refractory rickets, osteomalacia, osteitis fibrosa cystica and pathological fractures.
- *Persistent metabolic acidosis,* due to accumulation of non-volatile acids and loss of bicarbonates in urine.
- *Neurological manifestations*, e.g. altered behavior, ataxia, muscular weakness, neuropathy, often terminating in seizures and uremic coma, due to accumulation of toxic metabolites.
- *Recurrent infections,* due to granulocytopenia following bone marrow suppression.
- *Skin itching* due to uremic frost.
- *Cardiac dysfunction* due to cardiomyopathy, pericarditis or ventricular dysfunction may develop due to uremia, hypertension, fluid overload, dyselectrolytemia and vascular calcifications caused by mineral bone disease.

Laboratory evaluation of CKD includes:

- Complete urinalysis, including osmolality;
- *Hematological:* Hemoglobin, cell counts, platelet count;
- *Renal function tests:* BUN, S. Creatinine and S. Uric acid;
- Serum electrolytes" Na^+, K^+, Ca^{++}, PO_4^-- and alkaline phosphate;
- Blood gas analysis, including serum bicarbonates.
- Skeletal survey for osteodystrophy and rickets
- Renal imaging, e.g. USG and renal scan, if required.
- Renal biopsy for definitive diagnosis

Periodic assessment of these parameters is necessary to assess progression of disease.

Management of CKD is largely conservative and aims to retard progression of disease and improve the quality of life till renal transplant is possible. Important components of management include:

- **Nutrition:** Diet in CKD should provide 100–120% of recommended caloric requirements as condensed feeds, including high biological value proteins (1–2 gm/kg/day), fats mainly in polyunsaturated forms (e.g. MCT oils) and water-soluble vitamins. Protein restriction is not advisable unless BUN exceeds 80 mg/dl, to avoid endogenous breakdown of proteins.
- **Fluid and electrolyte management:** Sodium and water restriction is not necessary except in cases with hypertension or terminal ESRD, when sodium intake should be restricted to <1 gm/day. Potassium restriction is necessary only in cases of documented hyperkalemia, which may also be controlled by oral alkalinizing agents and potassium exchange resins (PO Kayoxalate 1 gm/kg/day). Diet containing high potassium items should be avoided.
- **Acidosis** is controlled with oral $NaHCO_3$ tablets (2–3 mEq/kg/day) with an aim to maintain serum bicarbonate levels >22 mEq/L. IV correction is advised if S. bicarbonate levels drop < 15 mEq/L.
- **Renal osteodystrophy** may be controlled by: (a) avoiding high-phosphorus foods, e.g. chocolates, dairy products, cola, etc., (b) use of phosphate-binders, e.g. calcium carbonate or Sevlamer hydrochloride (only in older children), (c) oral calcium supplements (0.5–2.0 gm/day), if hypocalcemia persists despite phosphate restriction, and (d) vitamin D supplements, preferably in active form (Rocaltrol 0.01–0.05 mg/kg/day) along with cholecalciferol.
- **Anemia** is usually corrected by iron and folic acid supplements. Blood transfusions should be avoided unless hemoglobin falls <6 gm/dl, to prevent sensitization as these patients are potential candidates of renal transplant. Recombinant erythropoietin (SC/IV 150–300 U/kg/week) is recommended in cases with Hb <10 gm/dl to minimize the need for transfusion. However, EPO therapy may not work in presence of uncorrected iron deficiency and secondary hyperparathyroidism.
- **Hypertension** in early stages may be treated with diuretics, salt-restricted diet and ACE inhibitors, e.g. enalapril or Angiotensin receptor blockers, e.g. Losartan, though these agents should be avoided once GFR fall <60/ml/kg/min. Calcium channel antagonists, e.g. Nifedipine or amlodipine, are preferred in cases with GFR <30 ml/min. Severe hypertension may require additional therapy with clonidine or pazocin.
- **Growth velocity,** apart from good diet, may be optimized by recombinant growth hormone therapy (SC 0.024 – 0.07 mg/kg/d), though high cost precludes its wider use.
- **Recurrent infections** need to be treated promptly, after modification of antibiotic doses as per creatinine levels. These children should also receive appropriate immunizations including those with HBV and all live vaccines in preparation for regular dialysis or renal transplant.
- **Renal replacement therapy (RRT):** Renal transplant and dialysis are two broad options for renal replacement therapy in ESRD and the choice of therapy and when to initiate it, depends on various clinical, biochemical, psychosocial and logistic factors. Renal transplant is always a preferred option for RRT, while Dialysis may be considered as a life-sustaining intervention till the transplant is possible.

Renal replacement therapy (RRT) should be considered when GFR falls <15 ml/min/1.73 m^2 and strongly recommended when it drops <8 ml/min/1.73 m^2, though the decision also depends on clinical status and presence of biochemical abnormalities.

Dialysis may be offered as continuous peritoneal dialysis (PD) or intermittent hemodialysis (HD), depending on the age and availability of procedure. Continuous PD is usually preferred in ESRD children <5 years due to difficulties in getting satisfactory vascular access.

- ***Continuous peritoneal dialysis*** can be provided at home through retention peritoneal catheters (e.g. Tenckhoff catheter), either as continuous ambulatory peritoneal dialysis (CAPD) or as intermittent cyclic peritoneal dialysis — manually or with the help of an automated device. Cycler-driven PD permits more freedom to the child who can continue to have normal activity in day-time and exchanges are performed automatically during sleep. Usually 4–6 cycles/day are necessary for satisfactory results. Peritonitis is a major complication, due to catheter-tunnel infections.
- ***Hemodialysis,*** usually twice or thrice a week, is more efficient option but requires adequate infrastructure, good vascular access and repeated hospital visits.

Renal transplantation (RT) is the treatment of choice in children with ESRD, using living-related donor (LRD-RT) or cadaveric kidneys (CAD-RT). Success rate depends on donor type, age of the recipient, and etiology of ESRD. Best results are obtained with LRD-RT, in children >2 years with non-hereditary disease.

Indications: Currently >60% of RT in children are performed for congenital or hereditary nephropathies. **Table 21.18** provides reasonable criteria for selection of prospective candidates for RT.

Procedure: In brief, important steps in RT include:

- Evaluation of prospective recipient and donor to exclude serious infections and systemic diseases, and ABO and HLA typing.
- Recipient-donor matching for ABO and HLA type, as well as direct cross-matching between recipient serum and donor T and B cells, to detect pre-formed antibodies—potential cause of early graft rejection.
- Actual transplant surgery, with intensive intra-operative asepsis and fluid-electrolyte control.
- Post-transplant immunosuppressive therapy to prevent graft rejection and anti-infection prophylaxis against opportunistic infections.

Outcome: Overall success rate and survival among pediatric renal recipients is ~92–95%, higher among the LRD-RT than in CAD-RT. Opportunistic infections during post-transplant immunosuppressive therapy is commonest cause of mortality in these cases, apart from other complications **(Table 21.19)**. Renal disease may recur in the transplanted kidney.

TABLE 21.18: Selection criteria for renal transplant

- Chronic renal failure/end-stage renal disease
- Age > 2 years and/or weight > 10 kg
- Absence of HIV, serious systemic illness, severe mental retardation and untreated malignancy
- Availability of suitable living related donor
- Ensured compliance for long-term management

TABLE 21.19: Complications of renal transplantation

Early	*Late*
Primary graft dysfunction	Recurrence of primary disease
Surgical complications	*Iatrogenic:* Growth failure, ↑ BP
Acute graft rejection	Delayed graft rejection
Opportunistic infections	Malignancy in new kidney

21.11 TUBULAR DISORDERS

Renal tubules are primary sites for-(a) concentration and dilution of urine, (b) reabsorption or secretion of various solutes, (b) net acid secretion to maintain normal acid-base balance.

Renal tubular disorders includes primary defects of the generalized or specific tubular functions, without significant impairment in glomerular/interstitial function. Some important tubular disorders are discussed here.

21.11.1 RENAL TUBULAR ACIDOSIS

Renal tubular acidosis (RTA) denotes impaired renal capacity for urinary acidification, due to either (a) inadequate reabsorption of bicarbonates or (b) secretion of acids (H^+ ions) in renal tubules, leading to a state of persistent metabolic acidosis (normal anion gap) with normal or near-normal GFR.

Pathophysiology: Kidneys is the prime regulator of normal acid-base balance by:

- Reabsorption of HCO_3^-, mainly in proximal tubules,
- Secretion of H^+ in distal tubules and collecting ducts.

About 85% of HCO_3^- are absorbed in proximal tubules with recycling of H^+- a process that needs adequate carbonic anhydrase activity **(Fig. 21.7)**. However, there is no net excretion of H^+ ions at proximal tubules level and hence, urine is not acidified here.

On the other hand, distal tubules and collecting ducts can retrieve only ~15% of bicarbonates but net H^+ secretion occurs here, leading to actual acidification of urine.

Consequently, RTA may be broadly divided into:

- Distal RTA or type I,
- Proximal RTA or type II,
- Hyperkalemic RTA or mineralocorticoid deficiency or type IV.

Type III RTA is a combination of type I and II RTA, not considered as a separate entity at present.

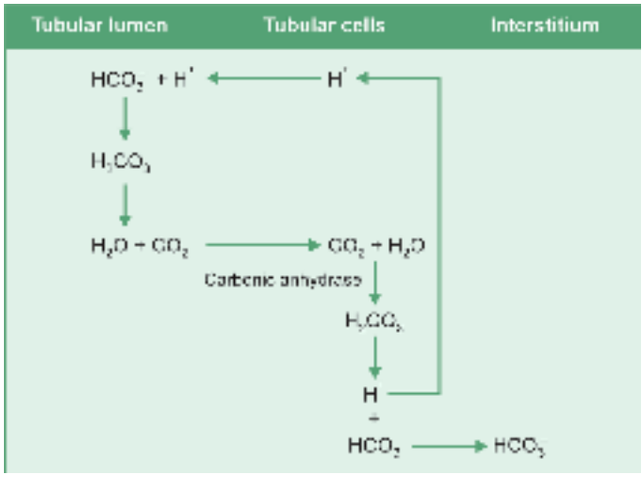

Fig. 21.7: **HCO_3 reabsorption in proximal tubules.**

- **Proximal RTA** is a severe defect due to near-complete loss of HCO_3^- reabsorption capacity, which cannot be compensated by distal tubules, leading to severe bicarbonaturia. However, urine is well acidified (pH <5.5) in these defects, due to intact distal tubular functions, i.e. H^+ secretion. Proximal RTA may be an isolated defect, or more commonly a part of generalized proximal tubular dysfunction (Fanconi syndrome) leading to proteinuria, aminoaciduria, glucosuria and other electrolyte wasting along with bicarbonaturia (Ch 21.11.2).
- **Distal RTA** is a milder defect due to minimal loss (10–15%) of HCO_3^- reabsorption capacity. However, urinary acidification is significantly impaired in these cases due to impaired H^+ secretion and urinary pH does not fall <5.5, despite severe systemic acidosis.
- **Type IV RTA,** due to impaired aldosterone production or renal responsiveness to aldosterone is characterized by impaired secretion of both H^+ and K^+ ions at distal nephrons, leading to acidosis and hyperkalemia.

Important metabolic defects in RTA include:

- *Persistent metabolic acidosis* due to excessive excretion of bicarbonates in urine and defective urine acidification;
- *Hyperchloremia* due to compensatory reabsorption of chloride ions;
- *Hypokalemia* due to entry of more $NaHCO_3$ (unabsorbed in proximal tubules) in distal tubules, which stimulates Na^+ absorption in exchange for K^+, in distal/collecting tubules. Hyperkalemia occurs in type IV RTA.

Etiology of RTA is heterogeneous and depends on the site of lesion **(Table 21.20)**. While isolated defects of proximal or distal RTA are known as sporadic or inherited disorders, most cases are part of generalized defects in tubular transport.

TABLE 21.20: Causes of renal tubular acidosis (RTA)

Distal RTA (Type I)
- Isolated (Sporadic, AD, AR)
- *Syndromic:* Familial hypercalciuria, Wilson disease
- Secondary
  - Interstitial nephritis, nephrocalcinosis, sickle cell disease
  - Reflux nephropathy and chronic pyelonephritis
  - *Drugs and toxins:* Amphotericin, Cisplatin

Proximal RTA (Type II)
- Isolated (sporadic or AR)
- Fanconi syndrome (Multiple tubular dysfunction)
  - Primary or inherited (AR, AD, XLR)
  - *Syndromic:* Cystinosis, Lowe syndrome
  - *Drugs:* aminoglycosides, Ifosfamide, cisplatin
  - *Toxins:* Lead or other heavy metals
  - *Others:* Myeloma, collagen disease, transplant rejection

Hyperkalemic RTA (Type IV) (Mineralocorticoid deficiency)
- *Primary:* Addison disease, CAH, hypoaldosteronism
- Pseudohypoaldosteronism (aldosterone resistance)
- *Secondary:*
  - Pyelonephritis, interstitial nephritis,
  - *Drugs:* Cotrimoxazole, cyclosporine

AR: Autosomal recessive; **AD:** Autosomal dominant; **XLR:** X-linked recessive; **CAH:** Congenital adrenal hyperplasia

TABLE 21.21: D/D proximal vs distal RTA

	Distal RTA	***Proximal RTA***
Plasma HCO_3	<10	>10
Urine pH	>5.5	<5.5
Urine anion gap	Positive	Negative
Urine Ca: Creatinine	Increased	Normal

Fanconi syndrome is the commonest cause of proximal RTA, while distal RTA is usually acquired after toxic renal injury or interstitial nephritis.

Clinically, inherited RTA defects present in late infancy, while acquired cases may present at any age depending on the cause. Important manifestations include:

- Progressive failure to thrive,
- Persistent metabolic acidosis,
- Polyuria with dehydration,
- Signs of hypokalemia, e.g. muscular weakness,
- Signs of primary disease, e.g. rickets,
- Signs of other metabolic defects, e.g. nephrocalcinosis due to hypercalciuria and hypercitraturia

Diagnosis of RTA should be suspected in any case of failure to thrive with typical biochemical abnormalities, i.e.: *(a) fluid-refractory metabolic acidosis, (b) low serum bicarbonate levels, (c) hyperchloremia and (d) hypokalemia;* after excluding more common causes, e.g. diarrhea.

Important laboratory differences between proximal RTA and distal RTA (are provided in **Table 21.21**.

Treatment of RTA aims to correct acidosis and maintain normal serum bicarbonate and potassium levels. After

initial parenteral correction of acid–base and electrolyte disturbances, long-term therapy includes:

- *Oral bicarbonate supplements* as *Shohl solution* (1 mEq/ml of bicarbonate equivalent) or *Sodium bicarbonate tablets* (3.4 mEq/300 mg tablets). Higher doses (5–20 mEq/kg/d) are required in proximal RTA or distal RTA in infancy, than distal RTA in older children (2–4 mEq/kg/d).
- *Oral potassium supplements* (2–4 mEq/kg/d) as *Kesol solution* (1 mEq/ml) in hypokalemic cases. Type IV RTA may need chronic treatment for hyperkalemia with sodium-potassium *exchange resin* (Kayexalate). Oral *Potrate* (potassium citrate) (1 ml = 2 mEq of K) has additional effect by improving the acidosis and the hypokalemia and is preferred alkali supplements
- *Other supplements,* e.g. vitamin D, phosphates, etc. may be required, specially in proximal RTA.
- Patients with distal RTA with symptomatic hypercalciuria (recurrent hematuria or nephrocalcinosis) may require *thiazide diuretics* to decrease urine calcium excretion.

Prognosis of RTA depends on the cause. Isolated proximal RTA, though more severe initially, may resolve in first decade but isolated distal RTA is a life-long disease.

21.11.2 HEREDITARY TUBULAR DISORDERS

While large number of inherited tubular disorders with defect in water or electrolyte conservation are known **(Table 21.5)**, important ones are as follows:

Fanconi syndrome is the generalized defect of proximal tubular transport, characterized by bicarbonaturia (proximal RTA), glucosuria, phosphaturia, tubular proteinuria, aminoaciduria and citrauria.

Etiology: Fanconi syndrome may be primary (sporadic or hereditary), or secondary (acquired). Important causes of secondary Fanconi syndrome include:

- *IEM:* Cystinosis, Wilson disease, Lowe syndrome*
- *Drugs:* Aminoglycosides, Cisplatin, Ifosfamide
- *Toxins:* Lead or other heavy metal poisonings
- *Others:* Myeloma, collagen disorders

*Lowe syndrome is a rare x-recessive disorder with congenital cataract, mental retardation and Fanconi syndrome.

Clinically, these cases present with short stature, failure to thrive, resistant rickets, recurrent vomiting and severe acidosis/electrolyte imbalance during intercurrent infections; apart from other features of causative disease.

Diagnosis rests on A constellation of biochemical abnormalities, e.g.—(a) hyperchloremic acidosis, (b) generalized aminoaciduria, (c) glycosuria, and (d) phosphaturia despiTe low serum phosphorus levels.

X-rays may reveal severe rickets or osteopenia. serum creatinine and renal USG is usually normal. All cases should also be investigated for primary cause.

Treatment includes: (a) alkali therapy as for proximal RTA (8–14 mEq/kg/d), (b) potassium supplements (2–4 mEq/kg/d), (c) phosphate supplements (50–75 mg/kg/d) as Joule's solution or Adphos sachets (30 mg/ml), and (d) vitamin D analogues in cases with rickets; along with treatment of primary disease. Oral hydrochlorothiazide (1–2 mg/kg/d) may be added in cases with persistently low bicarbonate levels despite alkali therapy. Thiazides cause extracellular volume contraction, thereby increasing the bicarbonate absorption in proximal tubules.

Cystinosis, an autosomal recessive disorder, is an important cause of secondary Fanconi syndrome and proximal RTA. It is characterized by generalized accumulation of cystine in various body tissues including kidneys, due to a membrane transport defect that prevents cystine excretion from cells.

Clinically, apart from features of Fanconi syndrome, diagnosis may be confirmed by detection of cystine crystals in cornea and measurement of leukocyte cystine content.

Treatment aims to correct metabolic abnormalities, along with life-long therapy with oral cysteamine that binds cystine to form excretable cysteine. Early initiation of this drug can delay the deterioration of renal function.

Idiopathic hypercalciuria is a common inherited defect of tubular calcium transport with reduced reabsorption, leading to hypercalciuria and consequent nephrocalcinosis.

Clinically, these cases present with recurrent gross or persistent microscopic hematuria, along with recurrent formation of renal calculi.

Diagnosis rests on 24-hour urinary calcium excretion (>4 mg/kg) or urinary calcium:creatinine ratio (>0.2), beyond infancy.

Treatment involves use of oral thiazide diuretics in symptomatic cases to reduce urinary calcium excretion by stimulating its reabsorption in distal tubules.

Nail-Patella syndrome is an autosomal dominant disorder with—(a) dystrophic nails, (b) absent/hypoplastic patella, and (c) chronic renal disease, characterized by impaired urinary concentration/acidification capacity, microscopic hematuria and/or proteinuria. Most cases run a benign course but 10–20% develop CKD in late life.

Bartter syndrome is a rare form of renal potassium wasting due to unexplained cause (probably secondary to a chloride reabsorption defect), biochemically characterized by—(a) persistent moderate hypokalemia, (b) high urinary potassium, and (c) hypochloremic metabolic alkalosis.

Clinically, it presents since infancy with growth failure, polyuria/polydipsia, recurrent dehydration and muscle weakness/cramps. Absence of hypertension (despite elevated renin) in a case of hypochloremic metabolic acidosis is an indicator of Bartter syndrome.

Treatment includes long-term oral potassium supplements with a potassium sparing diuretic, e.g. triamterene. Refractory cases may be treated with prostaglandin inhibitors, e.g. indomethacin.

Nephrogenic diabetes insipidus (DI) is characterized by complete or partial tubular unresponsiveness to antidiuretic hormone (ADH), leading to severe impairment in urinary concentration capacity. It may be primary (X-linked recessive) or secondary due to loss of medullary concentration capacity in renal failure, interstitial nephritis, obstructive uropathies, nephrocalcinosis, etc.

Clinically, primary nephrogenic DI usually presents in early infancy with polyuria, polydipsia and recurrent episodes of hypernatremic dehydration. Long-term complications include growth failure, mental retardation and hydronephrosis due to excessive urine production

Diagnosis is confirmed by *water deprivation test*, though formal test is not necessary in cases with serum osmolality of >290 mOsm/kg with simultaneous urine osmolality of <290 mOsm/kg. Further vasopressin challenge test is required to exclude central DI (Ch 22.2.4). Persistence of urine:plasma osmolality ratio <1, despite vasopressin challenge, indicates nephrogenic DI.

Management includes adequate fluid intake, low-salt diet and diuretic therapy. Paradoxical response to diuretic therapy (Hydrochlorothiazide 1–2 mg/kg/d) is probably due to sodium depletion after diuretics, which enhances absorption of sodium and water in proximal tubules.

21.11.3 ACUTE TUBULAR NECROSIS

Acute tubular necrosis (without arterial or glomerular lesions) is a common cause of intrinsic renal failure following—(a) sudden hypovolemia/shock, (b) nephrotoxic drug/chemical exposure or (c) infections. These patients usually present with a prolonged diuretic phase after initial oliguria, which can cause severe fluid and electrolyte disturbances.

21.12 ACUTE INTERSTITIAL NEPHRITIS

Acute interstitial nephritis or tubulointerstitial nephritis an inflammatory disorder of predominantly renal interstitium due to any cause, is an important cause of acute renal failure though some cases may present with chronic renal insufficiency.

Etiology: Leading causes of acute interstitial nephritis in childhood include—(a) drugs, e.g. NSAIDs, penicillin, sulfonamides and furosemide, (b) Systemic infections, e.g. diphtheria, leptospirosis, CMV, EBV, etc.

Chronic interstitial nephritis is seen in—(a) obstructive uropathy with vesicoureteric reflux, (b) prolonged analgesic abuse, and (c) systemic disorders, e.g. SLE or sickle cell disease.

Clinically, acute interstitial nephritis may present with rapidly progressive renal insufficiency with history of preceding drug/infection exposure, after 3–5 days of offending exposure.

Presentation of chronic disease is usually non-specific with progressive pallor, mild edema, headache, anorexia and recurrent abdominal pain.

Diagnosis must be suspected in any case of progressive renal insufficiency despite adequate urine output. Hyposthenuria and mild proteinuria is common. Presence of eosinophils in urine indicates drug-induced disease.

Renal biopsy is diagnostic and reveals focal or diffuse inflammatory reaction in interstitium, more prominent in peritubular region; with/without secondary involvement of tubules and rarely, glomeruli.

Management is non-specific and cause-related; including—(a) elimination of offending drug, (b) treatment of primary cause and (c) management of acute/chronic renal failure. Corticosteroid trial (PO Prednisolone 0.5–1 mg/kg/day) may be given if disease is remitting or prolonged.

21.13 URINARY TRACT MALFORMATIONS

Urinary tract malformations are commonest cause of obstructive uropathy in children. Early diagnosis of these defects by prenatal or neonatal ultrasonography is important to prevent secondary effects, e.g. obstructive uropathy, vesicoureteric reflux, recurrent UTI and occasionally, post-renal failure.

Embryology: Urinary tract develops from:

- Mesonephric duct, which arise from lower allantois, just above the terminal end of primitive hindgut, i.e. cloaca; and
- Primitive urogenital sinus, which is formed after division of cloaca by a transverse urogenital septum into anterior urogenital sinus and posterior cloacal sinus (ano-rectal canal).

Ultimately, (a) ureters develop from a ureteric bud of mesonephric duct, (b) trigone of bladder from lower part of mesonephric duct, incorporated into urogenital sinus, (c) urinary bladder (except trigone) from upper part of primitive urogenital sinus, and (d) urethra from lower part of urogenital sinus.

Upper part of mesonephric duct, above the origin of ureteric bud, becomes atretic to form urachus—a ligament between bladder and umbilicus. Urinary tract anomalies may be classified according to the site of

TABLE 21.22: Common urinary tract malformations

- **Pelviureteric junction (PUJ) anomalies**
  - Infundibular stenosis (hydrocalycosis)
  - Kinks, bands and strictures
- **Ureteric anomalies**
  - *Abnormal number:* Agenesis, duplication
  - *Abnormal location:* Ectopic ureters
  - *Abnormal size:* Megaureter, ureterocele
- **Urinary bladder anomalies**
  - Agenesis/hypoplasia
  - Exstrophy of bladder (Ectopia vesicae)
- **Uretheral anomalies**
  - Posterior urethral valves
  - Hypospadias/Epispadias

obstruction **(Table 21.22)**, of which some common ones are discussed here.

Pelvi-ureteric junction (PUJ) anomalies: PUJ malformations, though more common in males, are commonest cause of obstructive uropathy in females and second commonest in males (after posterior urethral valves).

PUJ anomalies are more common on left side and include a spectrum of defects—intramural defects, e.g. stenosis, persistence of fetal folds, aperistaltic segment, etc. or extrinsic defects, e.g. aberrant vessels, ectopic kidneys.

Clinically, these cases may be picked up on antenatal USG (fetal hydronephrosis) or manifest later with palpable renal mass, hematuria after trivial trauma, recurrent UTI and occasionally, intermittent Dietl's crisis (sudden abdominal pain with renal lump due to ? torsion of pelvis).

Diagnosis rests on USG to show pelvic dilatation without ureteric dilatation, though a DTPA/MAG-3 scan is necessary to exclude milder abnormalities. IVP, though not necessary, shows pelvis dilatation with abrupt cut-off at PUJ.

Treatment: Early surgical repair is indicated in cases with bilateral disease, solitary kidney or severe hydronephrosis with worsening functions. In others, follow-up is advisable as mild to moderate fetal hydronephrosis is known to improve with time.

Posterior urethral valves (PU valves) are the commonest cause of obstructive uropathy in male infants, seen in 1:5000 to 1:8000 children.

Pathogenesis: PU valves are located just distal to the verumontanum at the junction of anterior and posterior urethra. Embryologically, these structures are considered as—(a) extreme development of normal urethral folds and ridges, or (b) remnant of the urogenital membrane.

These valves act as a rigid membrane causing obstruction to the urinary outflow, followed by elongation and fusiform dilatation of the proximal urethra. Depending on the severity of lesion, back-pressure leads to variable degree of detrusor muscle hypertrophy, secondary VUR and hydronephrosis.

PUV are also classified as-*Type I*, which radiate distally from verumontanum and merge to form anterior commissure; *Type II*, which spread proximally and usually remain undetected; and rare *Type III*, consisting of a diaphragm with central hole and require retrograde catheterization.

Clinically age of presentation depends on the severity of the obstruction.

Severe cases present in neonatal period with-(a) acute urinary retention with distended bladder, (b) enlarged/palpable kidneys, (c) urinary ascites and (d) respiratory distress due to associated pulmonary hypoplasia.

Moderate lesions present later with—(a) weak urinary stream, (b) intermittent urinary retention, (c) obstructive uropathy and renal failure, (d) repeated UTI.

Diagnosis: *Micturating cystourethrography* (MCU) is the investigation of choice for postnatal diagnosis, which shows a dilated posterior urethra, poor flow to distal urethra, residual urine with secondary bladder abnormalities and vesicoureteric reflux.

PU valves may be diagnosed on prenatal USG, which also reveals distended bladder, bilateral hydroureter and hydronephrosis. Oligohydramnios and consequent pulmonary hypoplasia is common.

Antenatally suspected PUV should be confirmed postnatally by USG on Day 3 of life, based on bilateral hydronephroureterosis and thickened distended bladder with dilated proximal urethra (Key-hole sign).

Treatment: Endoscopic fulguration of valve leaflets using a diathermy current, is the treatment of choice in PU valves. However in cases with severe renal insufficiency, initial stabilization with fluid and electrolyte correction, control of urinary infection and temporary drainage of urine (catheter or vesicostomy) is necessary before surgery.

Post-surgery, serial USG monitoring and antimicrobial prophylaxis may be needed in cases with significant vesicoureteral reflux, along with DMSA scan. Bladder dysfunction is common and many cases need intermittent catheterization and bladder augmentation procedures.

Prognosis: While renal functions improve rapidly after surgery, ultimate outcome depends on severity of pre-surgical renal impairment and reduction of serum creatinine levels after surgery. Prognosis is good if post-surgery serum creatinine falls <0.8 to 1 mg/dl. Cases with severe obstructive uropathy or delayed surgery may progress to chronic renal failure, requiring renal transplantation. Urinary incontinence is common even after successful surgery.

Prune-Belly syndrome is a characteristic triad of—(a) deficient abdominal muscles, (b) undescended testes

Fig. 21.8: **Prune-belly syndrome.**

and (c) urinary tract anomalies, e.g. megaureters, megabladder, patent urachus, etc.

Oligohydramnios and pulmonary hypoplasia is common and ~ 95% cases are males. Prognosis depends on the severity of pulmonary hypoplasia and renal dysplasia. While ~1/3rd cases die in utero or within few weeks, another 1/3rd progress to end-stage renal disease **(Fig. 21.8)**.

Bladder exstrophy is a rare (1:40,000 births) malformation with variable severity, ranging from merely epispadias or small vesicocutaneous fistula in abdominal wall, to complete ectopia vesicae.

Embryologically, these anomalies indicate complete/partial failure of urogenital septum to connect with cephalad part of cloacal membrane.

In classic cases, bladder protrudes from abdominal wall with exposed mucosa and complete epispadias. Pubic rami and recti muscles are widely separated and anus is anteriorly displaced. Undescended testes and inguinal hernia are common.

Management involves multi-stage reconstructive surgery including closure of exstrophic bladder at birth, correction of epispadias after infancy and lastly, the reconstructive surgery to achieve continence.

However, post-surgical complications are common and include—(a) urinary incontinence, (b) recurrent UTI, (c) sexual dysfunction, and (d) risk of bladder cancers in later life.

Hypospadias is the commonest congenital anomaly of urethra, characterized by abnormal urethral meatus opening on the ventral surface of penile shaft rather than on the glans-tip, with or without chordee (abnormal ventral curvature of the penis) and underdeveloped prepuce.

Although usually an isolated defect, many cases are associated with other anomalies of genitourinary tract, e.g. undescended testis, inguinal hernia, vesicoureteric reflux, etc.

TABLE 21.23: Classification of hypospadias

Anterior hypospadias (80–85%)
- Glandular
- Coronal
- Sub-coronal or distal penile

Middle hypospadias (10–15%)
- Mid-penile

Posterior hypospadias (3–6%)
- Proximal penile
- Peno-scrotal
- Scrotal
- Perineal

Fig. 21.9: **Hypospadias.**

Incidence is estimated to be ~1:250–500 male births, more common in newborns with in utero estrogen exposure.

Clinical presentation of hypospadias depends on the location of the urethral orifice **(Table 21.23)**. Depending on the severity of abnormality, these cases present with-(a) asymptomatic cosmetic defect, (b) abnormal urinary stream with ventral deflection or splaying, (c) sexual dysfunction due to chordee, and (d) features of co-anomalies, e.g. obstructive uropathy **(Fig. 21.9)**.

Diagnosis is clinical, though radiological evaluation of whole urinary tract is necessary to exclude co-existing urinary tract and renal anomalies. Cases with severe hypospadias should also be differentiated with ambiguous genitalia by karyotyping.

Management aims to correct cosmetic as well as function deformity with surgical repair, best started at 6–12 months of age. Although the type of surgery depends on the location of meatus, general principles include—(a) meatoplasty, (b) urethroplasty, and (c) correction of chordee.

Complication rate of surgery varies from 5 to 15%, including urethrocutaneous fistula, meatal stenosis, urethral strictures/diverticula and wound infection.

Epispadias, i.e. urethral meatus opening on the dorsal surface of penis, is relatively less common than hypospadias and frequently associated with short, upturned penis and urinary incontinence.

Based on the site of the meatal opening, epispadias is classified as—*glandular, penile or penopubic.*

In females, similar displacement of urethral meatus may present with bifid clitoris, flattening of the mons and labial separation, classified as—*minimal* (Patulous urethral opening), *intermediate* (dorsally split urethra along most of its length) or *severe* (complete urethral cleft with incompetent sphincter).

Management depends on the severity, with surgical repair involving meatostomy, urethrostomy and release of dorsal chordee (*Cantwell-Ransley repair* or corpora-corporal anastamosis), usually at the age of 2 years.

21.14 OBSTRUCTIVE UROPATHY

Obstructive uropathy, the commonest cause of chronic renal failure in children, is characterized by urinary obstruction at any level from calyceal infundibula to urethral meatus, and its pathophysiological effects on renal functions.

Etiology: Although obstructive uropathy is a consequence of many congenital or acquired lesions of urinary tree **(Table 21.24)**, posterior urethral valve is the commonest cause in boys, while In girls, PUJ obstruction is most common.

Pathophysiological effects of obstruction depend on its site, cause, severity and age of onset. While urethral or bladder obstruction present with acute urinary retention, obstructions above the level of bladder cause unilateral hydronephrosis, which manifests after many years or remains undetected throughout life.

Obstruction of urinary tract at any site ultimately affects renal functions by—(a) back pressure and dilatation of proximal tract, (b) urinary stasis with increased risk of UTI and stones. While early changes are reversible, prolonged obstruction may lead to progressive and irreversible damage to renal architecture and function.

TABLE 21.24: Causes of obstructive uropathy

1. *Congenital anomalies:*
   - Posterior urethral valves
   - Pelviureteric junction obstruction
   - Vesicoureteric reflux
   - *Others:* aberrant vessels
2. Calculi
3. Neurogenic bladder
4. Retroperitoneal fibrosis
5. Post-inflammatory: UTI, TB
6. Surgical/traumatic injury

Clinical presentation: Urinary tract obstruction may be silent or present with:

- Micturation problems, e.g. retention, weak stream, incontinence, etc.
- Recurrent UTI with fever, dysuria, etc.,
- Hydronephrosis with renal mass, hematuria, etc.
- Renal colic due to stones or Dietal's crisis,
- Signs of chronic renal failure, e.g. failure to thrive.

Diagnosis: USG is the baseline investigation to detect obstructive uropathy and hydronephrosis, including for prenatal diagnosis. However, the mild pelvicalyceal dilatation is common at birth and USG should be repeated after 48 hours and then periodically. Fetal hydronephrosis with pelvic diameter >12 mm is unlikely to be physiological.

Postnatal assessment of hydronephrosis on USG needs detailed investigations to identify the cause of obstruction, status of renal functions and progression of the disease, by:

- Voiding cystourethrography in bilateral hydronephrosis to detect VUR and PU valves,
- Renal scintigraphy, i.e. DMSA scan and MAG-3 (with diuretic renogram) to assess renal functions.
- Urodynamic studies, e.g. Whitaker test in equivocal cases
- Other investigations, e.g. spinal X-ray/MRI to exclude neuropathic bladder and cystoscopy to visualize uretero-vesical abnormalities.

Management depends on the cause of obstruction and status of renal functions. Before any surgical intervention, it is mandatory to—(a) assess the functional status of other kidney and expected benefits from surgery, (b) exclude or treat co-existing UTI, and (c) manage other complications, e.g. hypertension or chronic renal failure.

Posterior urethral valves and pelviureteric junction obstruction are commonest causes of obstructive uropathy in males and female children respectively, discussed earlier in Ch 21.13. Some other important causes of obstructive uropathy are as follows:

Vesicoureteral reflux (VUR), i.e. retrograde flow of the urine from bladder to the ureter and renal pelvis, is the cause as well as effect of obstructive uropathy. It is seen in ~1% of normal children and >30–35% of those with febrile UTI.

Etiology: VUR may be primary or secondary.

- *Primary VUR* denotes a congenital anomaly at ureterovesical junction that allows urinary backflow, e.g. (a) shorter intravesical ureteric tunnel, (b) impaired flap-valve mechanism, or (c) ectopic ureter, etc. Primary VUR is a leading cause of prenatal hydronephrosis in males, which is frequently inherited, seen in 35% siblings and 50% offsprings.
- *Secondary VUR* is a consequence of distal obstructive uropathy, e.g. in PU valves, bladder neck obstruction or neurogenic bladder. In later case, VUR may develop without urinary obstruction.

TABLE 21.25: International classification of VUR

Grade	*USG/IVP finding*
I	Partial filling (<1/3rd) of undilated ureter
II	Filling (>1/3rd) but undilated upper urinary tract*
III	Dilatation of ureters and upper urinary tract*
IV	Tortuous ureters + III above
V	Gross dilatation/tortuosity of whole urinary tract, Loss of papillary impression

*up to pelvis and calyces.

Clinical course: VUR is often discovered as an underlying abnormality during investigations for obstructive uropathy, recurrent UTI, hypertension, chronic renal disease or prenatal hydronephrosis. Further course depends on it severity **(Table 21.25)** and age of presentation.

Primary VUR may resolve spontaneously if-mild (<Grade II), unilateral or diagnosed at younger age. Spontaneous resolution is unlikely beyond 5 years.

Severe/persistent VUR may lead to recurrent or persistent pyelonephritis due to ascending infection, consequent renal scarring with progressive renal insufficiency. Reflux nephropathy is characterized by renal cortical scarring, predominantly at the poles, leading to hypertension and renal failure.

Diagnosis of VUR includes—(a) detection and grading of severity, (b) identification of etiology, and (c) assessment of secondary renal damage, e.g. obstructive uropathy and renal scarring.

USG is the baseline investigation to detect pre-/postnatal VUR that reveals—(a) dilatation of urinary tract, (b) actual ureteral reflux during voiding phase on flow-Doppler study, (c) renal scarring. However, USG cannot exclude mild VUR.

Confirmation of diagnosis usually rests on—(a) voiding cystourethrography (MCU) for direct visualization of reflux, or (b) radionuclide cystography to detect renal scarring and pyelonephritis. Urodynamic studies and uroflowmetry are indicated in suspected neuropathic bladder. Cystoscopy helps to directly visualize ureteric or bladder abnormalities.

Management depends on the severity of reflux, age of the patient and presence of bladder bowel dysfunction (BBD).

- *Low-grade VUR (I and II) without bladder-bowel dysfunction* (BBD) do not need any intervention, while others should receive antibiotic prophylaxis till resolution of BBD.
- *High-grade VUR (≥ III)* need antibiotic prophylaxis for (a) 1 year after last UTI attack or till 2 years of age in absence of BBD, or (b) till resolution of BBD. Repeat imaging is indicated in these cases after 24–36 months, preferably with radionuclide cystogram.

Early surgical correction is indicated in—(a) severe VUR >grade III, (b) recurrent UTI despite prophylactic antibiotics, (c) progressive renal insufficiency. Apart from treatment of primary cause, VUR surgery involves lengthening of intramural ureter or creating a flap-like mechanism to establish an effective valvular mechanism (uretero-neocystostomy). Open surgical repair is effective in 80–95%. Endoscopic repair by subtrigonal injection of a bulking agent under ureteric orifice to create artificial flap-valve, is an alternative but less effective (60–80%) option.

Urinary prophylaxis: Single bed-time dose of oral cotrimoxazole (1–2 mg/kg), nitrofurantoin (1–2 mg/kg), cephalaxin (10 mg/kg) or cephadroxil (5 mg/kg) may be used for prophylaxis, though first two drugs are contraindicated in infants < 3 months or G6PD deficiency.

All siblings should also be screening for VUR by USG, in view of the strong hereditary risk.

Outcome: Primary VUR usually resolves by 6–10 years in 70–90% cases with grade I or II severity and 10–35% in higher grade VURs.

Neuropathic bladder: Urinary bladder function is regulated by three neural mechanisms—(a) excitatory parasympathetic flow (S2–3), (b) inhibitory sympathetic flow (L1–2), and (c) Voluntary corticospinal flow.

Clinically, according to the site of lesion, neuropathic bladder may present as:

- Urinary retention due to predominant loss of excitatory parasympathetic flow, e.g. in sacral injury.
- Urinary incontinence, due to predominant loss of sympathetic outflow, e.g. in lumbar or cauda equine lesions.
- Reflex bladder in cortical or high spinal lesions with intermittent involuntary evacuation without voluntary control.

Etiology: Neuropathic bladder denotes voiding abnormalities due to spinal cord lesions like: (a) congenital defects, e.g. meningomyelocele, sacral agenesis, etc. (b) traumatic spinal injuries, and (c) spinal tumors.

Important consequences of neuropathic bladder are urinary incontinence, recurrent UTI, obstructive uropathy and vesicoureteral reflux.

Evaluation of these cases must include: (a) urodynamic studies to assess bladder volume and voiding pressure, (b) uroimaging to assess the secondary hydronephrosis, VUR, etc., (c) urine cultures to exclude UTI, and (d) evaluation of primary cause.

Treatment includes: (a) reduction of bladder pressure with anticholinergics, e.g. oxybutynin and intermittent catheterization, (b) long-term antimicrobial prophylaxis, and (c) surgical correction, i.e. augumentation enterocystoplasty in severe cases.

Nephrolithiasis (renal calculi), is relatively less common in children than in adults, contributing ~5% of obstructive uropathy. Calcium phosphates or oxalates stones account for >70% of urinary stones in childhood, followed by struvite stones of magnesium ammonium phosphate (~20%), uric acid stones (<5%) and rarely, cystine stones (<1%). Underlying metabolic abnormality is present in ~50% cases.

Nephrocalcinosis refers formation of crystalline deposits within renal parenchyma, usually detected on ultrasonography.

Etiologically, important contributory factors for urolithiasis are:

- Increased urinary excretion of solutes, e.g. calcium, oxalates, cystine, uric acid etc,
- Impaired stability of solutes due to abnormal urine pH (cystine in acidic pH, phosphates in alkaline pH),
- Decreased excretion of solute-binders, e.g. magnesium, citrate, etc.
- Urinary stasis with solute concentration, and
- Urinary infection, specially with proteus infection.

While important causes of urinary calculi are given in **Table 21.26**, idiopathic hypercalciuria is the commonest cause of calcium stones in children (Ch 21.11.2).

Clinically, these cases may be entirely asymptomatic or present at any age with—(a) recurrent painful hematuria, (b) abdominal flank pain or typical renal colic, (c) intermittent/acute urinary retention, (d) passage of stone/gravel in urine, and (e) signs of causative disease.

Diagnosis involves visualization of stone and etiological evaluation by:

- *Radioimaging:* While >90% stones are radio-opaque (except pure uric acid and cystine stones) visible on X-rays, USG is the preferred choice to detect small or radiolucent stones, as well as to exclude co-existing obstructive uropathy.
- *Metabolic screening*, e.g. estimation of 24-hour urinary excretion for calcium, phosphate, oxalate, uric acid, along with simultaneous serum levels. Serum vitamin D and parathormone levels should also be assessed.
- *Microbial evaluation* for associated UTI.
- *Examination of stone* passed in urine.

TABLE 21.26: Predisposing factors for urolithiaisis

- **Metabolic causes**
  - *Hypercalciuria*
    - Idiopathic hypercalciuria*
    - Renal tubular acidosis*
    - Hypercalcemic states (↑ PTH, Vitamin D toxicity)
    - *Others:* Prolonged immobilization, steroids
  - *Hyperoxaluria* (primary, malabsorption)
  - *Hyperuricemia* (cytotoxic therapy, gout)
  - *Cystinuria* (hereditary)
- **Urinary tract infection**
- **Urinary stasis** *(obstructive uropathy)*
- **Foreign body,** e.g. prolonged catheterization
- **Idiopathic** - *Endemic vesical stones*

*despite normal or low serum calcium levels

TABLE 21.27: Prevention of metabolic urinary stones

For calcium stones
- Restricted dietary intake
- Thiazide diuretics to decrease Ca^{++} excretion
- Inhibitors - citrates, e.g. lemonades, K^+ citrate

For uric acid stones
- Urinary alkalinization ($NaHCO_3$/Na citrate)
- Allopurinol therapy

For cystine stones
- Urinary alkalinization
- Chelators - D-penicillamine, N-acetylcystine

For oxalic acid stones
- Restricted dietary intake
- *Inhibitor:* K^+citrate, pyridoxine

Management depends on the location, size and composition of stone as well as presence of obstruction and infection. Medical management includes use of high volume fluid therapy with use of diuretic flush therapy.

While very small stones (5–7 mm) may pass spontaneously, percutaneous or laparoscopic surgical removal or extracorporeal shock wave lithotripsy (ESWL) is indicated in—(a) large or impacted stones, (b) recurrent ureteric colic/hematuria, or (c) progressive hydronephrosis. α-adrenergic blockers, e.g. tamsulosin, may facilitate passage of small stones by relaxing the ureter below the stone. In some cases, a ureteral stent may be passed endoscopically to dilate the ureter and allow the calculus to pass.

Preventive measures include—(a) ensuring high fluid intake, (b) treatment of underlying metabolic problem **(Table 21.27)** and (c) prophylactic long-term antimicrobial therapy in selected cases.

21.15 URINARY TRACT INFECTIONS

Urinary tract is the third commonest site of infection in children after gut and respiratory tract, involving lower urinary tract (cystitis) or upper urinary tract (pyelonephritis), or both.

Urinary tract infection (UTI) is defined as the growth of a significant number of microorganisms of a single species in the urine, in presence of symptoms.

Prevalence: About 1–2% boys and 3–7% girls experience at least one attack of symptomatic UTI by 6 years of age. In addition, asymptomatic bacteriuria is seen in 1–3% of infants, pre-school children and school-age girls (not boys).

While in neonatal period, UTI is more common in males (5:1) due to higher incidence of congenital urinary

tract anomalies, sex distribution equals in infancy, followed by marked female preponderance in older children/adolescence (1:10) due to shorter urethra and poor perineal hygiene.

Predisposing factors: Three most important predisposing factors for UTI are—(a) *urinary stasis* or obstruction, (b) *ascending infection* due to vesicoureteric reflux or repeated catheterization, and (c) poor *perineal hygiene*, e.g. pin-worm infestation or constipation **(Table 21.28)**. Obstructive lesions are present in 10–20% of cases with recurrent UTI.

Etiopathogenesis: UIT is predominantly an ascending infection from periurethral flora, except in newborns and infants, where renal parenchyma may be directly infected during septicemia from distant sites (hematogenous spread).

Common causative pathogens for UTI include:

- *Gram-ve: E. coli*, Klebsiella, Proteus, Pseudomonas
- *Gram +ve: Staph. epidermidis, Strept. faecalis*
- *Others:* Candida, Adenovirus (cystitis)

Over 75% of community-acquired UTI are due to *E. coli*, while nosocomial infections are usually caused by Klebsiella, Pseudomonas, Candida or Gram-positive pathogens. Proteus infection is more common in males.

Clinically, UTI may present as—(a) asymptomatic bacteriuria (positive urine culture, without symptoms), (b) symptomatic lower UTI or cystitis, (c) upper UTI or pyelonephritis, or (d) chronic or recurrent UTI.

Cystitis, presents with urinary complaints, e.g. dysuria, frequency, urgency, incontinence and suprapubic pain. Fever is uncommon. Most UTIs in first 5 years of life have associated upper UTI or pyelonephritis.

Pyelonephritis, the most serious form, presents as high fever with chills, nausea/vomiting, and abdominal flank pain. In newborns, it may also presents as septicemia, e.g. fever/hypothermia, poor feeding, diarrhea/vomiting, unexplained jaundice, shock, etc.

Chronic Or recurrent UTI may be asymptomatic or presents with failure to thrive, prolonged pyrexia and occasionally hypertension due to post-infective renal scarring, apart from recurrent attacks of acute UTI.

UTI is also classified as—(a) ***complicated,*** in presence of high fever, persistent vomiting, dehydration, systemic toxicity, renal angle tenderness or elevated creatinine values, or (b) ***uncomplicated*** or simple, in absence of these features.

Laboratory diagnosis of UTI may be divided into three stages—(a) diagnostic confirmation of UTI, (b) d/d between upper and lower UTI, and (c) identification of underlying pathology.

(a) Diagnosis of UTI rests on the presence of pus cells and bacteria in urine, followed by confirmation on urine culture **(Table 21.29)**.

- ***Presumptive diagnosis*** can be made in presence of significant pyuria, i.e. >10 cells/mm^3 in uncentrifuged or > 5 cells/hpf in centrifuged urine sample.

  However, isolated pyuria without bacteriuria does not necessarily indicate UTI and may occur in any febrile illness, renal tuberculosis, interstitial nephritis or schistosomiasis. Similarly, absence of pyuria does not exclude UTI as frequent voiding in infants may not allow sufficient stay of urine in bladder to form pus cells. Pyuria may also be absent due to disintegration of cells on delayed urinalysis or poor inflammatory response in immunodeficient hosts.

  Rapid Dipstick tests based on detection of nitrites or Leukocyte esterase in urine are useful screening test to detect presence of bacteria or pus cells in urine respectively. However, a positive dipstick test should always be confirmed by urine culture.
- ***Microbiological confirmation*** requires urine culture from a sample, collected by (a) *suprapubic puncture* (most reliable but invasive), (b) *urethral catheter* (specially in infants when suprapubic puncture is not possible), and (c) *mid-stream clean-catch* method in older toilet-trained children. Cultures from urine bags or diapers are not acceptable. Specimen should

TABLE 21.28: Predisposing factors for UTI

- **Urinary stasis**
  - Obstructive uropathy
    - Congenital anomalies of urinary tract
    - Neurogenic bladder
    - Others, e.g. stones
  - Voluntary urine retention in females
- **Easy ascend of infection**
  - Short urethra in females
  - Vesicoureteric reflux (VUR)
  - Urinary catheterization
- **Altered perineal flora**
  - Un-circumcised males
  - Constipation/encopresis
  - Pin-worm infestation
  - Poor hygiene, e.g. tight underwear
  - Prolonged antibiotic therapy

TABLE 21.29: Diagnostic indicators for UTI

Supportive (urine examination):

- ***Significant pyuria****
  > 10 WBCs/mm^3 (uncentrifuged sample)
  > 5 WBCs/HPF (centrifuged sample)
- ***Positive dipstick test***

Confirmatory (urine culture):

- Supra-pubic puncture : Any colony count
- Urethral catheter : Colony count > 5×10^4 cfu/ml
- Mid-stream clean-catch : Colony count > 10×10^5 cfu/ml

be processed within an hour of collection but may stored at 4°C up to 24 hours. Interpretation of culture reports depends on the method by which sample was collected **(Table 21.29)**. Urine culture must be repeated in clinical suspected cases of UTI with unequivocal colony count or polymicrobial growths.

(b) Differentiation between upper and lower UTI in children is difficult in children and not essential for treatment purpose, though involvement of upper urinary tract (pyelonephritis) is indicated by presence of: (a) high fever/toxemia, (b) positive blood culture, and (c) antibody-coated bacteria in urine.

(c) Identification of underlying pathology: Asymptomatic bacteriuria, even if persistent, does not require detailed investigations except USG, as it is often caused by persistence of low-virulence, non-invasive *E. coli*, without underlying anatomical/functional defect.

Further evaluation for underlying pathology is indicated in all cases of UTI, though may be deferred till second attack in older girls with simple uncomplicated UTI. Imaging studies include: (a) USG for structural malformations, VUR and renal scarring, (b) MCU for obstructive uropathy or vesicoureteric reflux, and (c) DMSA scan to assess renal scarring and excretory function. However, the need for each investigation varies with age.

- *Children <5 years* with first attack of UTI must be screened with USG soon after the diagnosis and those with abnormal USG or recurrent *non-E. coli* UTI must be investigated by MCU after 2–4 weeks and DMSA after 4–6 months.
- *Children >5 years* must be screened with USG and further evaluation with MCU is needed only in those with abnormal USG and recurrent UTI. DMSA is not routinely advised in older children.

Management: No treatment is needed for asymptomatic bacteriuria except periodic urinalysis, which usually resolves in 6 months without renal scarring.

Management of symptomatic UTI may be divided into—(a) treatment of acute attacks, (b) treatment of underlying cause, and (c) prevention of recurrent attacks.

Management of acute attack includes supportive therapy and specific antibiotics **(Table 21.30)**.

Antibiotic therapy: While simple or uncomplicated UTI in children >3 months may be treated with oral antibiotics for 5–7 days, complicated attacks or any attack <3 months of age, need parenteral therapy for at least first 48–72 hours, followed by completion with oral antibiotics for total 7–10 days (10–14 days in infants).

Urine culture should be repeated after completion of treatment to exclude persistent infection. Complicated UTI, which does not respond to IV antibiotics in 48 hours, must be reassessed with USG and repeat urine culture.

TABLE 21.30: Treatment of choice for UTI

Uncomplicated UTI (PO × 7–10 days)	
• Cefexime	8–10 mg/kg/d q12 hr
• Coamoxiclav	30–40 mg/kg/d q12 hr
• Cotrimoxazole	6–10 mg/kg/d q12 hr
• Ciprofloxacin	10–20 mg/kg/d q 12 hr
• Ofloxacin	15–20 mg mg/kg/d q 12 hr
• Cephalexin	50–70 mg/kg/d q8-12hr
Complicated UTI (IV for 48–72 hrs > PO 10–14 days)	
• Ceftriaxone	50–75 mg/kg/d q12–24 hr
• Cefotaxime	100–150 mg/kg/d q8–12 hr
• Amikacin	10–15 mg/kg/d q24 hr
• Gentamycin	5–6 mg/kg/d q24 hr
• Ampicillin	100 mg/kg/d q6–8 hr

Supportive therapy in UTI includes—(a) plenty of oral fluids to dilute infection, (b) frequent emptying of bladder, and (c) Symptomatic antipyretics and antispasmodics to relive pain/fever. Urine alkalinizing agents may be used to relieve dysuria, though no necessary in all cases.

Prevention of recurrent UTI: Apart from correction of predisposing factors, e.g. obstructive lesions, long-term antimicrobial prophylaxis is indicated in—(a) all children with high grade VUR, (b) all infants with any VUR, and (c) all children with recurrent febrile UTI, specially in presence of bladder-bowel dysfunction.

Single bed-time dose of oral cotrimoxazole (1–2 mg/kg), nitrofurantoin (1–2 mg/kg) or cephalexin (10 mg/kg) or cefadroxil (5mg/kg) may be used for prophylaxis, though first-two drugs must be avoided in infants < 3 months or G6PD deficiency.

Antibiotic prophylaxis must be continued in infants till 2 years of age or at least 1 year after the last attack, and in older children till resolution of VUR or bladder bowel dysfunction.

Outcome of UTI depends on presence/absence of underlying pathology and secondary renal damage before diagnosis. Each attack of UTI may accentuate renal scarring with consequent risk of hypertension and chronic renal insufficiency in later life.

Genitourinary Tract Tuberculosis

Genitourinary tuberculosis is uncommon in childhood, usually seen after more than 5 years of primary infection.

Infection is acquired hematogenously and preferentially localized at—(a) juxtamedullary region, (b) trigone/periuretetic region of bladder, (c) prostrate in males and fallopian tubes (90%) in females.

Pathologically, renal lesions may persist as asymptomatic granuloma or progress with caseation/fibrosis to cause—(a) hydronephrosis/pyonephrosis, (b) perinephric abscess, (c) renal cavity, (d) miliary lesions, or (e) ureteric deformities. Renal failure is rare.

Symptomatic cases may present with—(a) painless hematuria, or (b) recurrent UTI or pyuria without bacteriuria, and (c) sterility.

Diagnosis rests on positive urine culture or molecular diagnosis and treatment includes specific antitubercular therapy (Ch 10.13) as per sensitivity profile, along with supportive measures.

21.16 PENOSCROTAL DISORDERS

Penoscrotal disorders may be congenital or acquired. This chapter deals with some important penosrcotal problem in children excluding penile malformations, i.e. epispadias/hypospadias, discussed earlier (Ch 21.13) and urogenital infections, which are more frequent in adolescents and discussed in Ch 13.3.

Cryptorchidism (undescended testis): Testes in early fetal life develop intra-abdominally and descend subsequently into scrotum, guided by its anchor – Gubernaculum. Testicular descent is controlled by various mechanical factors, i.e. intra-abdominal pressure, gubernacular-pull, etc. as well as hormonal factors, i.e. testosterone, dihydrotestosterone and Mullerian-inhibiting factor.

Cryptorchidism (absence of testes in scrotum) represents complete/partial failure of normal testicular descent, arrested at any point along the normal path, i.e. abdomen (15%), inguinal canal (80–85%) or rarely migrated to ectopic sites, e.g. perineum (<5%).

Incidence: Cryptorchidism is present in ~4–5% of term newborns and in <1% at 1 year of age. As the testicular descent mainly occurs in last trimester, incidence is naturally higher in preterms.

Etiology: Various factors, implicated in the etiology of undescended testis include—(a) mechanical factors, e.g. Inguinal hernia, abnormal gubernaculum; (b) hormonal factors, e.g. androgen deficiency or insensitivity, and (c) abnormalities of epididymis or genitofemoral nerve.

Clinically, cryptorchidism is usually unilateral (80–90%). True undescended testis must be differentiated from retractile testis, i.e. testis palpable in inguinal canal, but can be pulled down into scrotum. Retractile testis is not uncommon due to overactive cremasteric reflex in older boys and hence, should be examined in squatting position. Indirect inguinal hernia is common with cryptorchidism **(Fig. 21.10)**.

Complications: Undescended testis is essentially normal at birth but develops progressive pathological changes, due to higher temperature and other factors operative at ectopic sites. Common complications include:

- *Infertility,* more common in bilateral (~40–50%) than unilateral (~10–15%) cryptorchidism. However, children operated before 2 years usually retain normal testicular functions.

Fig. 21.10A and B: Cryptorchidism: (A) Bilateral; (B) Unilateral.

- *Testicular malignancy* in 3rd/4th decade is ~10 times more common in undescending testis.
- *Testicular torsion* with/without infarction.

Diagnosis is largely clinical, though investigations are needed to—(a) locate abdominal testis by USG, MRI or laparoscopy, and (b) to exclude anorchia (absent testis), by hormonal tests, e.g. FSH, LH and testosterone levels after HCG stimulation.

Treatment: As ~80% of undescended testis, specially those in inguinal canal, descend spontaneously in infancy, surgery is deferred till 9–15 months. However, further delay is not advisable due to risk of irreversible pathological changes, which may affect fertility.

Orchidopexy with closure of indirect hernia is the treatment of choice in most cases. Two-stage orchiopexy may be needed for high abdominal testis. Hormonal treatment with human chorionic gonadotropin (hCG) or gonadotropin releasing hormone (GnRH) may be tried to facilitate testicular descent in cases with low/retractile testes with limited success.

Orchiectomy is indicated in children with delayed diagnosis (>2 years) and non-functioning testis, to reduce the risk of malignancy in later life. Buserelin (a GnRH analogue) may be used in selected cases with delayed orchidectomy, to normalized testicular histopathology, though with variable results.

Hydrocele, i.e. accumulation of fluid in the tunica vaginalis, may be congenital or acquired.

Etiology: Most cases of childhood hydrocele are congenital due to persistent patency of processus vaginalis, which may/may not be communicating with abdomen at the time of diagnosis. Acquired hydrocele, although uncommon, may be due to testicular torsion, epididymitis, trauma or tumors. Filaria-a common cause of hydrocele in Indian adults, is uncommon in childhood.

Clinically, hydrocele presents as a smooth, non-tender, trans-illuminating scrotal swelling. Communicating hydrocele is often associated with indirect inguinal hernia and reducible on pressure **(Fig. 21.11)**.

Fig. 21.11: **Congenital hydrocele.**

Management: Non-communicating hydrocele usually absorbs spontaneously by 12 months of age and Surgical drainage is indicated only in—(a) hydrocele persisting >12 months, (b) large/tense swellings, and (c) acquired hydrocele. Congenital communicating hydrocele requires ligation of processus vaginalis with herniorrhaphy.

Varicocele, i.e. abnormal dilatation of pampiniform venous plexus of scrotum due to valvular incompetence of spermatic vein is rare before adolescence and should raise a possibility of retro-peritoneal mass.

These cases present with painless para-testicular mass with 'bag of worms' feel on palpation which becomes prominent on erect position.

Varicocelectomy is indicated only in children with large varicocele or significant disparity in testicular size.

Micropenis is defined as the normally formed penis, but with stretched penile length of < 2 SD below the mean size for age (< 1.9 cm in newborns).

It is caused by hormonal deficiency after the first trimester, due to: (a) hypogonadotropic hypogonadism, e.g. in Lawrence-Moon-Biedl syndrome, Prader-Willi syndrome, etc. (b) hypergonadotropic hypogonadism, i.e. primary testicular failure, and (c) idiopathic micropenis.

Evaluation includes karyotyping and endocrinal studies to assess pituitary and testicular functions. Androgenic hormonal therapy may be useful in some cases, though most cases achieve normal sexual function even without therapy.

Inflammatory penile disorders of penis or scrotum in children are generally infective or traumatic in origin. Some important disorders include:

Phimosis, i.e. inability to retract the prepuce, is physiological at birth, that corrects spontaneously by 3 years of age in >90% cases. In older boys, it may be: (a) congenital, (b) secondary to prepuceal infection/inflammation with scarring, or (c) post-circumcision. True phimosis is uncommon and occurs due to recurrent balanoposthitis causing fibrous rings.

No treatment is needed for physiological phimosis, except frequent cleaning of sub-prepuceal debris. In older children, local application of a steroid cream for 1–2 months may loosen the phimotic ring sufficiently to enable prepuceal retraction.

Circumcision on medical grounds is recommended only in—(a) phimosis persisting beyond 10 years or (b) ballooning of prepuce during micturation, and (c) associated paraphimosis.

Role of preventive circumcision in infancy to reduce the risk of—(a) secondary balanoposthitis and phimosis, (b) obstructive uropathy or UTI, (c) sexually transmitted diseases, e.g. HIV, and (d) penile carcinoma in later life, is highly controversial.

Common complications of circumcision include: (i) local bleeding, (ii) wound infection, (iii) secondary phimosis, and (iv) meatal stenosis. It is contraindicated in micro-penis, to spare extra skin for later reconstructive surgery.

Paraphimosis, i.e. retraction of prepuceal skin behind the coronal sulcus that can't be pulled back over glans, is a more serious problem, leading to painful venous stasis in the foreskin with edema. Treatment includes gentle stretching of prepuceal skin after lubrication, though emergency circumcision may be required.

Meatal stenosis is rarely primary, usually develops after circumcision due to inflammation of denuded glans. These cases present with dysuria and thin urinary stream with recurrent urethritis, urinary stasis and urinary tract infection.

Serial dilation of meatus is recommended as initial treatment, while resistant cases may need meatotomy or meatoplasty.

Scrotal swellings/masses may be acute or chronic, painless or painful **(Table 21.31)**. Diagnosis is usually established by clinical evaluation, USG and testicular flow scan (^{99m}Tc-pertechnectate) to establish vascular flow (absent in torsion, increased in inflammatory conditions). Some important causes are as follows.

TABLE 21.31: Causes of scrotal swelling or mass

Painless	*Painful*
• Hydrocele • Inguinal hernia • Varicocele • Tumors • Nephrotic syndrome	• Testicular torsion of: – Spermatic cord – Appendix of testis • Epididymo-orchitis • Traumatic hematoma • Orchitis, e.g. in mumps • Incarcerated ing. hernia

Testicular torsion of spermatic cord is the commonest cause of acute, painful, scrotal swelling in adolescents (rare <10 years), due to abnormal fixation of testis in the scrotum. Absent cremasteric reflex is strongly indicative of testicular torsion.

As the vascular flow to testis is rapidly interrupted in these cases, Immediate surgical de-torsion with refixation is essential within 6 hours, for survival of gonads.

Torsion of testicular appendix is the commonest cause of acute scrotum < 2 years, rare in adolescents (d/d torsion of spermatic cord). Testicular blood flow is usually maintained in this condition and spontaneous recovery with conservative management is common.

Epididymo-orchitis is the principle cause of acute painful scrotal swelling in adolescents, usually suggestive of sexually transmitted diseases, e.g. gonorrhoea or chlamydial infections. Epididymitis is rare before puberty and indicates possibility of an underlying Wolffian duct anomaly.

Testicular tumors may develop at any age including newborns. Nearly 2/3rd of them are malignant (germ cell tumors) and present as painless, hard testicular mass without transillumination.

Diagnosis rests on USG-guided FNAC or biopsy, along with serum tumor markers. Radical orchidectomy is essential in most cases.

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CHAPTER 22

Disorders of Endocrine System

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22.1 BASIC CONSIDERATIONS

Hormones are products of various endocrine (ductless) glands, secreted directly into circulation for transport to target organs. Biochemically, there are three major classes of hormones: (a) steroids, derived from cholesterol, e.g. adrenal-cortical hormones, (b) polypeptide proteins, e.g. pituitary and parathyroid hormones, and (c) tyrosine derivatives, e.g. thyroid and adrenal medullary hormones.

Although present in miniscule amounts, hormones are prime regulator of various metabolic and homeostatic activities. All hormones exert their biochemical action by binding with either extracellular receptors (peptide hormones) or intracellular receptors (steroid or thyroid hormones) on target organ. Absence or non-responsiveness of these receptors is an important cause of clinical hormonal deficiency, despite normal or elevated blood levels.

Endocrine system includes three separate but inter-dependent components in order of supremacy, i.e. hypothalamus, pituitary and target endocrinal gland; each regulating the function of descendent gland in most (but not all) cases. At the same time, circulating levels of hormones from target gland also provides a positive or negative feedback to hypothalamus and regulate its endocrinal activity.

Hypothalamus-hypophyseal Axis: Hypothalamus is the supreme regulator for most of the endocrine functions and controls functions of anterior pituitary by secreting various neuropeptides, i.e. releasing/inhibiting hormones or factors **(Table 22.1)**. It also synthesizes two direct-acting hormones-oxytocin and vasopressin. While hormonal Releasing/inhibitory factors are transported to anterior pituitary via minute capillary network (hypothalamic hypophyseal portal circulation), oxytocin and vasopressin are transported via axons to posterior pituitary for storage and release.

All neurohormones of hypothalamus are rapid but short-acting and release of them is controlled by many neurosensory inputs, higher function commands and circulating levels of target-endocrine hormone. Since hypothalamus also controls many other body functions apart from endocrinal activity, i.e. sleep, hunger, thirst, sexual behavior and emotional response; hypothalamic causes of endocrinal disturbances are frequently associated with simultaneous disturbances in these functions. Common causes of hypothalamic dysfunction include developmental malformations or acquired lesions due to tumors, trauma, irradiation and infections.

TABLE 22.1: Neurohormones of hypothalamus

Releasing factors or Hormones
- Thyrotropin releasing hormone (TRH)
- Corticotropin releasing hormone (CRH)
- Growth hormone releasing hormone (GHRH, Ghrelin)
- Gonadotropin releasing hormone (GnRH)
- MSH-releasing hormone (MSH-RH)

Inhibiting factors or Hormones
- Growth hormone inhibiting Hormone (GHIH or Somatostatin)
- Prolactin inhibiting factor (Dopamine)
- MSH-inhibiting factor (MSH-IF)

Hormones synthesized for posterior pituitary
- Vasopressin or anti-diuretic hormone (ADH)
- Oxytocin

MSH: Melanocyte stimulating hormone

22.2 PITUITARY DISORDERS

Pituitary (hypophysis) is a vital link in neuro-endocrinal system, consisting of two embryologically and functionally separate parts-anterior pituitary and posterior pituitary (neurohypophysis).

Anterior pituitary is derived from Rathke's pouch as an invagination of oral ectoderm and secretes seven different hormones **(Table 22.2)**, which either regulate other endocrine glands or act directly on target organs, e.g. breast, melanocytes and gonads. Of these, MSH is structurally a part of ACTH (first 13 amino acids, no corticotrophin activity), and currently, ACTH, rather than MSH, is considered as the regulator of melanocyte function and pigmentation.

TABLE 22.2: Pituitary hormones

Anterior pituitary *(synthesis and release)*
- Growth hormone (GH)
- Thyroid stimulating hormone (TSH)
- Adrenocorticotropic hormone (ACTH)
- Follicle stimulating hormone (FSH)
- Luteinizing hormone (LH)
- Prolactin (PRL)
- Melanocyte stimulating hormone (MSH)*

Posterior pituitary *(storage and release)*
- Oxytocin
- Vasopressin or ADH

**See* text

Posterior pituitary is connected with hypothalamus via nerve fibers and stores primary hormones synthesized in hypothalamus, i.e. oxytocin and vasopressin. Release of these hormones is mainly regulated by higher neurological centers and changes in body homeostasis.

22.2.1 HYPOPITUITARISM

Hypopituitarism may be limited to single hormonal deficiency (commonest-Isolated GH deficiency) or involves multiple pituitary hormone deficiency (MPHD)

Etiology: Hypopituitarism may be congenital or acquired **(Table 22.3)**. Apart from primary pituitary lesions, similar abnormalities are also caused by deficiency of corresponding releasing factor due to hypothalamic lesions or end-organ resistance despite normal hormonal levels.

Clinical manifestations of hypopituitarism depend on the spectrum of hormonal deficiencies and the age of onset.

- *Congenital hypopituitarism* may present at birth with micropenis or hypoplastic labia minora, hypoglycemia or prolonged jaundice or subsequently with—(a) short stature with lower growth velocity and delayed bone age, (b) facial dysmorphism with frontal prominence, saddle nose, prominent eyes, midfacial hypoplasia, small hands and feet and delayed dentition, and (c) absent/delayed sexual maturation. Intelligence is usually normal.
- *Acquired hypopituitarism* presents at any age with arrested physical growth and sexual maturation, as well as features of multiple endocrine deficiencies (hypothyroidism, hypoadrenalism) and causative intracranial lesions (e.g. raised intracranial pressure, localizing signs).

Diagnosis depends on pituitary/target endocrinal hormone assays, response to hypothalamic hormones, e.g. failed GH stimulation test, low Free T4 and TSH and low cortisol and ACTH levels as well as radioimaging studies for intracranial lesions.

Treatment includes management of primary causes, e.g. tumor, as well as hormone replacement therapy, depending on the needs. Treatment of GH deficiency is discussed in next section.

TABLE 22.3: Causes of hypopituitarism

a. Developmental defects (Pituitary a-/hypoplasia)
- With/without CNS abnormalities
- Due to hypothalamic defects
- Empty sella syndrome

b. Genetic hormonal synthesis defects
- Isolated growth hormone (GH) deficiency
- Multiple hormonal deficiencies

c. Destructive lesions (acquired)
- *Tumors:* Craniopharyngioma
- *Trauma:* Basal fractures, surgery, radiation
- Hypoxic/vascular injuries
- *Infiltrative:* Histiocytosis

d. End-organ resistance
- GH receptor defects (Laron dwarfism)
- Insulin-like growth factor (IGF) deficiency

22.2.2 GROWTH HORMONE DEFICIENCY

Growth hormone (GH) deficiency is a leading cause of short stature in childhood.

GH secretion is regulated by two important hypothalamic hormones – GHRH (releasing hormone, Ghrelin) and GHIH (inhibiting hormone, somatostatin). Alternate secretion of these two regulators is responsible for characteristic pulsatile release and diurnal rhythm in GH secretion, being highest during night. GH secretion is stimulated by sleep, exercise and hypoglycemia and inhibited by steroids, which also oppose its action on target tissues.

GH acts on various tissues by increasing the synthesis of an insulin-like growth factor (IGF_1) in liver and growth plates. Another mediator, IGF_2 has been identified as an important mitogen in bone cells with uncertain role.

Etiology: While GH deficiency is usually a part of MPHD in acquired lesions, isolated deficiency (IGHD) is more common, which is usually genetic and may be quantitative or qualitative. Common causes of IGHD include:

- Genetic or quantitative IGHD (AR, AD or X-linked)
- Biologically-inactive GH (qualitative defect)
- GH-receptor insensitivity (Laron syndrome)
- IGF_1 deficiency (IGF_1 gene or receptor defects)

Genetic causes involve either GH1 or GHRHR gene defects, which may be autosomal recessive, dominant or X-linked recessive.

Clinically, these cases have normal length at birth but intermittent episodes of hypoglycemia are common in neonatal period and infancy.

Most cases present beyond first year of life with—(a) proportionate severe short stature due to lower growth velocity, (b) doll-like appearance due to truncal obesity,

TABLE 22.4: Diagnostic criteria for GH deficiency

- Short stature (Height <3 SD)
- Poor growth velocity (<25th centile)
- Delayed bone age (but more than height age)
- Peak growth hormone levels < 7 ng/ml
- Low IGF-1 or IGFBP-3 levels*
- Resumption of growth on GH therapy

***IGFBP:** Insulin Like Growth Factor Binding Protein

midfacial hypoplasia, micropenis/hypoplastic labia and small hands/feet, (c) delayed bone age, but more than height age, (d) normal intelligence, and (e) delayed onset of puberty.

Mid-line defects, e.g. septum pellucidum, optic nerve hypoplasia and cleft palate may be seen, particularly in genetic forms. Delayed skeletal maturation permits linear growth to continue well beyond the usual age of completion and partly compensate for poor growth velocity in early life.

Diagnosis must be suspected on the basis of short stature with delayed bone age and needs to be confirmed by GH assays **(Table 22.4)**.

Considering diurnal variations, random GH levels are unreliable. IGF-1 and IGF binding proteins-(IGFBP-3) are useful screening tests but affected by malnutrition and systemic disorders. Provocation or stimulation tests after administration of clonidine, insulin, L-dopa, arginine or glucagon etc. are necessary for confirmation. While no single test is foolproof, peak GH levels of <7 ng/ml on two different provocation tests are highly suggestive of GH deficiency.

GH levels are elevated or normal in qualitative/receptor defects. Low IGF1 and IGFBP-3 levels with normal/high GH levels suggest GH-nonresponsiveness, e.g. Laron syndrome.

Relevant investigations with neuroimaging studies are also indicated to exclude secondary causes of hypopituitarism.

D/D of GH deficiency includes other causes of short stature (Ch 3.3) and MPHD (abnormal TSH and ACTH levels). Laron syndrome is an important cause of short stature due to end-organ resistance and does not respond to GH therapy.

Management: Availability of recombinant growth hormone preparations has improved outcome of GH deficiency and treatment should be started as soon as possible as daily night injections (25–50 µg/kg, subcutaneously). Higher doses may be used during puberty. Therapy should continue till the bone age exceeds 14 years in girls and 16 years in boys or growth velocity falls to <2 cm/year or desired height is achieved, whichever is earlier.

Maximum response is seen in first year of therapy, which may decrease in later years due to normalization of growth or development of antibodies. Pseudotumor cerebri is significant but rare complication of GH therapy. Rare side-effects include fluid retention, impaired glucose tolerance, worsening of scoliosis and slipped capital femoral epiphysis. Very rarely, there is increased risk of malignancy in some predisposed genetic conditions.

GH therapy is currently also recommended to enhance growth in many other non-GH deficiency short statures, e.g. chronic renal disease, intrauterine growth retardation, Turner syndrome, Noonan syndrome, Prader-Wili syndrome, and idiopathic short stature. Recombinant IGF1 is also available for treatment of IGHD due to hypothalamic causes and IGF1 deficiency.

22.2.3 HYPERPITUITARISM

Hyperpituitarism in children is very rare and caused by hormone-secreting adenomas, commonest being prolactinoma, followed by corticotropinoma, somatotropinoma and rarely thyrotropinoma or gonadotropinoma.

Clinically, most cases present either with only tall stature or broad-spectrum syndromes, e.g. acromegaly or gigantism. Gigantism is caused by overproduction of GH before the closure of epiphyses in younger children (less common), while acromegaly is a feature of late disease after closure of epiphysis. Consequently, gigantism is mainly characterized by tall stature while following features are more common in acromegaly:

- Tall stature, often with kyphosis.
- Typical facial features with macrocrania, broad nose, long tongue and prognathia with separation of teeth.
- Disproportionately long and thick fingers/toes.
- Neurological problems, e.g. visual field defects, raised ICP, behavioral problems.

Diagnosis depends on: (a) elevated GH levels (usually >400 ng/ml), which cannot be suppressed below 5 ng/ml on glucose suppression test, (b) elevated IGF1 and IGFBP-3 levels, and (c) neuroimaging to delineate the tumor. Levels of other pituitary hormones are often reduced with/without clinical manifestations due to destruction of anterior pituitary by growing adenoma.

D/D includes other causes of tall stature (Ch 3.4), the closest being cerebral gigantism.

Cerebral gigantism (Soto's syndrome) is an unexplained, probably hypothalamic, disorder, characterized by rapid linear growth from birth to 3–4 years of age, macrocrania, intellectual disability, gait abnormalities and normal or precocious puberty. GH levels are essentially normal and unlike pituitary gigantism, bone age is usually delayed.

Management includes removal of adenoma by surgery or irradiation. Octreotide (IM 1–40 µg/kg/d)-a synthetic somatostatin analogue is very effective to suppress GH secretion and reduce the tumor size. Pegvisomant (SC 10–30 mg/d), a GH-receptor antagonist, has also been successfully used in adults.

22.2.4 DIABETES INSIPIDUS

Antidiuretic hormone (ADH) or vasopressin is a peptide, synthesized in hypothalamus and transported to posterior pituitary for storage and subsequent release. It primarily acts on renal collecting ducts to enhance water reabsorption in response to changes in plasma osmolality.

Diabetes insipidius (DI) is characterized by reduced ADH activity, leading to polyuria (>2000 ml/m^2/day or >5 ml/kg/hour), polydipsia and their consequences.

Etiologically, DI is either inherited or acquired and may be divided as: (a) central DI due to lack of ADH secretion, or (b) nephrogenic DI due to nonresponsiveness of renal tubular cells to ADH.

Central DI is rarely a primary genetic defect, usually caused by involvement of hypothalamus/posterior pituitary region in: (a) tumors, e.g. craniopharyngioma, (b) neurosurgery, (c) infective/infiltrative diseases, e.g. intracranial infections, histiocytosis, and (d) other pathologies, e.g. birth asphyxia, etc.

Nephrogenic DI may be inherited (X-linked recessive), or more likely, acquired due to renal damage in: (a) drug-toxicity, e.g. lithium, (b) hereditary nephropathies, e.g. hypercalcemia/hypokalemia, polycystic disease, etc., and (c) renal tubular injury, e.g. chronic pyelonephritis, sickle cell disease, etc.

Clinically, polyuria and polydipsia are hallmark of DI and most cases present with features of:

- Cellular dehydration, e.g. failure to thrive, recurrent fever, mental retardation,
- Relative hypernatremia, e.g. irritability and behavioral changes,
- Polyuria, i.e. nocturnal enuresis, disturbed sleep,
- Co-existing endocrinal disorders (central DI)

D/D of DI includes other causes of polyuria, e.g. compulsive water drinking, diabetes mellitus, hypercalcemia, hypokalemia, etc.

Diagnosis depends on:

- *Persistently low urinary osmolality* (<300 mOsm/kg) with high serum osmolality (>300 mOsm/kg). In borderline cases with serum osmolality between 270–300 mOsm/kg, water deprivation test (discussed below) is indicated to confirm the diagnosis.
- *Water-deprivation test* helps to differentiate DI from compulsive water drinking. After overnight fast of 6 hours, normal child can concentrate the urine above 900 mOsm/kg. Inability to concentrate beyond 300 mOsm/kg indicates complete DI, while those with partial defects may concentrate up to 300–900 mOsm/kg.
- *Vasopressin-challenge test* helps to differentiate central DI from nephrogenic DI. More than 50% improvement in urinary osmolality after one hour of desmopressin nasal spray (10–20 µg) administration indicates central DI, while <50% change suggests nephrogenic DI.
- Other investigations include neuroimaging of the brain to exclude pituitary lesion and electrolyte monitoring.

Management: Intranasal administration of Desmopressin or DDAVP (1-desamino-8-d-arginine vasopressin) in individually tailored dose (5–10 µg/day q12–24 hr) is the treatment of choice for *central DI*. Oral DDAVP (25–300 µg/dose q8–12hr) may be used as an alternative. Central DI following neurosurgery is best managed with IV vasopressin infusion (1.5 mU/kg/hr) in acute phase.

Nephrogenic DI is managed with: (a) liberal and sufficient fluid intake, (b) sodium-restricted diet, and (c) thiazides diuretics (PO Hydrochlorothiazide 2–4 mg/kg/day) or Indomethacin (PO 2 mg/kg/day) in divided doses. Exact mechanism for this paradoxical effect of thiazide diuretics is unknown, perhaps related to diuretic-induced sodium depletion leading to compensatory increase in sodium absorption along with water. High-dose DDAVP therapy may be useful in some cases.

22.2.5 SYNDROME OF INAPPROPRIATE ADH SECRETION (SIADH)

SIADH is a common and important cause of dys-electrolytemia in critical care units, denoting "disproportionately high plasma ADH levels as compared to plasma osmolality, leading to excessive urinary concentration, fluid retention and dilutional hyponatremia".

Etiologically SIADH is either due to increased ADH secretion from hypothalalmus or secretion of other ADH-like vasopeptides from neoplastic tissues. SIADH is commonly seen in:

- Acute CNS disorders, e.g. intracranial infections, head injury, subarachnoid hemorrhage, etc.
- Critically sick children due to any cause, e.g. pneumonia, post-surgery, invasive ventilation, etc.
- Neoplastic states, e.g. leukemia, lung and pancreatic tumors, etc.

Clinical manifestations are often dominated by features of causative disease, along with:

- Signs of water intoxication, e.g. vomiting/nausea and irritability,
- Signs of hyponatremia, e.g. seizures, stupor or coma.

Diagnosis of SIADH should be suspected in any critically sick baby with: (a) hyponatremia, and (b) high urine osmolality despite low serum osmolality.

Management includes: (a) Restricted fluid intake to only 2/3rd of maintenance requirements, (b) correction of hyponatremia and other electrolyte abnormalities, and (c) treatment of primary cause.

Demeclocycline, which blocks the ADH action on collecting tubules, may be used in selected cases. Vasopressin receptor antagonists, i.e. Conivaptan or Tolvaptan also increase free water clearance.

22.3 THYROID DISORDERS

Primary function of thyroid gland is to synthesize and store two important hormones—Thyroxin (T_4) and Tri-iodotyrosine (T_3), later being 3–4 times more metabolically potent than the former. Only 20% of circulating T_3 is directly secreted from thyroid. Rest is produced by de-iodination of T_4 in peripheral tissues, mainly liver and kidneys.

Physiology: Important steps in thyroidal hormonal synthesis are:

a. Transport of dietary iodine (as iodide) and trapping into thyroid tissue, using an energy dependent sodium-iodide symporter mechanism;
b. Organification (oxidation) of trapped iodide into iodine, catalyzed by thyroidal peroxidase enzyme;
c. Iodination of tyrosine (secreted from thyroid cells as a specific thyroprotein) to produce monoiodotyrosine (MIT) and diiodotyrosine (DIT);
d. Coupling of 2 DIT molecules to form T_4 and one DIT and one MIT molecule to form T_3;
e. Storage of T_4 and T_3, as thyroglobulin in thyroid follicles;
f. Liberation of T_4 and T_3 from thyroglobulin and release in circulation, as and when needed.

Release of these hormones from thyroid is regulated by pituitary TSH, which is inturn controlled by hypothalamic TRH. TRH and consequently TSH production is increased in thyroid deficiency states (positive feedback) and inhibited by hormonal excess (negative feedback).

In circulation, more than 99% of T_4 and T_3 is bound to various carrier proteins, most important being thyroxin-binding globulin (TBG). Most of the T_3 in circulation is produced by peripheral conversion of T_4 by the enzyme monodeiodinase. Physiological effects are mediated after their uptake by target cells with specific thyroid hormone receptors.

22.3.1 HYPOTHYROIDISM

Hypothyroidism is a functional defect with decreased thyroid hormone activity, either due to deficient production or defective cell-receptors. It may be congenital or acquired and goiterous or non-goiterous. Common causes of hypothyroidism have been enlisted in **Table 22.5** while some important and common causes in childhood are as follows:

Congenital hypothyroidism (CH) is the commonest preventable cause of intellectual disability in Indian children, though the incidence has declined in developed countries due to neonatal screening programs. Early diagnosis and management of congenital hypothyroidism is essential to avoid permanent growth and mental retardation, as ~70% of brain growth is over by the end of neonatal period.

CH may be transient or permanent. Transient hypothyroidism is caused by blocking of receptors by maternal antibodies or antithyroid medications in mother.

Etiology: CH may be (a) primary (~95%) due to thyroid dysgenesis, dyshormonogenesis or TSH receptor resistance, or (b) secondary (~5%) to hypothalamic or pituitary causes and very rarely, (c) peripheral due to thyroxine resistance.

Thyroid dysgenesis accounts for >90% cases of CH, including total thyroid aplasia (~30%), partial agenesis or ectopic thyroid tissue. Depending on the severity, these cases manifest in neonatal period or after many years.

Maternal iodine deficiency or endemic goiter, specially in sub-Himalayan region, is another important cause of CH in India, though the incidence has declined due to widespread use of Iodized salts.

Thyroxin synthesis defects are all characterized by goiterous hypothyroidism. Commonest of them being peroxidase deficiency, which prevent organification of trapped iodide into iodine.

Among the genetic factors, CH is known to be associated with TSHR, PAX8 and TSHB genes. Pendred

TABLE 22.5: Causes of hypothyroidism

Congenital	*Acquired*
• TRH deficiency/unresponsiveness • TSH deficiency/unresponsiveness • Thyroid dysgenesis (aplasia, ectopia) • Defective thyroxin synthesis – Iodine transport defect – Thyroxine peroxidase deficiency – Pendred syndrome – Thyroglobulin synthesis defects – De-iodination defects • Intrauterine injury (maternal influences) – Radio iodine/irradiation exposure – Antithyroid/iodine therapy – Endemic goiter/iodine deficiency • TRB Antibodies (Maternal autoimmune disorders)	• Autoimmune thyroiditis – Hashimoto disease – Polyglandular autoimmune syndromes • Hypothalamic tumors (craniopharyngioma) • Hypopituitarism • Iodine deficiency (endemic goiter) – Neurologic – Myxedematous • Iatrogenic – *Drug:* Amiodarone, iodides, antithyroids – Radiation exposure, radio iodine therapy – Thyroidectomy • Infiltrative diseases—histiocytosis • Thyroid receptor non-responsiveness

syndrome is characterized by goiter and sensorineural deafness, due to iodine-transport defect in thyroid gland and chloride-transport defect in ears.

Clinical manifestations vary according to the severity of etiological defect and most cases are asymptomatic at birth. Wide-open posterior fontanel is the only consistent, but not pathognomonic feature at birth (also seen in preterms).

Clinical features of CH may be divided into *early features* recognizable at birth or in neonatal period and *classical clinical picture* that develops only after 8–10 weeks **(Table 22.6)**.

Typical facial features in a classic case include coarse, dull and puffy face, narrow palpebral fissure due to myxedematous eyelids, protruding tongue and depressed nasal bridge **(Fig. 22.1A)**.

Diagnosis: Confirmation of CH depends on-a) TSH >20 IU/L before 2 weeks of age or >10 IU/L after 2 weeks, b) Low T4 <10 µg/dl, or c) Low free T4 <1.17 ng/dl. However, TSH criteria cannot be used for diagnosis of the rare cases of central hypothyroidism due to hypothalamic/ pituitary causes, which have low TSH levels.

Neonatal screening programs use TSH estimation from the dried blood spot (DBS) sample collected after 72 hours of birth, though cord blood sample may also be used. TSH levels >40 IU/L in first 7 days of life, >20 IU/L between 7–21 days and >10 IU/L afterwards suggest the need to start treatment, while waiting for confirmation.

Ultrasonography and *Radionuclide scan* (^{123}Tc-sodium iodide) are required to confirm thyroid agenesis, dysgenesis or ectopia (decreased uptake), which also helps to differentiate these anatomical defects form two other common cause of CH – Iodine deficiency and hormone synthesis defects (normal or increased uptake). However, treatment must not be delayed for reports to avoid adverse effects on the developing brain.

TABLE 22.6: Clinical features of congenital hypothyroidism

Early neonatal
- Wide-open posterior fontanel
- Prolonged jaundice
- Constipation
- Feeding/breathing difficulties
- Sluggish activity and feeble cry
- Umbilical hernia
- Hypothermia

Established case (after 8–10 weeks)
- Stunted growth (short limb-short stature)
- Typical facial appearance
- Coarse, scanty hair with low hairline
- Thick, broad neck, supraclavicular fat pad
- Broad and short hands
- Dry, thick, scaly skin with less perspiration
- Delayed motor/mental development
- Generalized hypotonia
- Delayed relaxation of deep tendon reflexes
- Delayed dentition and bone age
- Bradycardia

Fig. 22.1A and B: Cretinism: (A) Facial appearance; (B) absence of ossification centers at knee.

CH may also be suspected on the basis of *delayed skeletal maturation*, i.e. absence of ossification centers for lower femur and upper tibia on knee X-ray in newborns **(Fig. 22.1B)** and lesser number of carpal bone centers on hand X-rays in older children. Other important radiological changes include-epiphyseal dysgenesis/ punctate epiphysis on limb X-rays, wide fontanels/ sutures and intrasutural wormian bones on skull X-rays, and deformity/beaking of T_{12} or $L_{1–2}$.

Management: Oral sodium L-thyroxine (Eltroxin) is the drug of choice, started as 10–15 µg/kg in newborns and then the dose is titrated according to clinical response and hormone assays. T_4/FT_4 and TSH levels are expected to normalize by one week and four weeks respectively, though all cases should be monitored at least every 2 months in first two years. Relief of constipation is a good indicator of clinical response in most cases.

Usually, smaller doses are required in older children (4 µg/kg) in the beginning, to be titrated up over 3–4 weeks. Side-effects are dose-related and include tachycardia, headache, hyperactive behavior and features of hyperthroidism.

Life-long therapy is needed for thyroid dysgenesis or synthesis defects. In undiagnosed etiology, a therapeutic test may be attempted by stopping the drug for 2–3 weeks, after 3 years of age. Rapid rise of TSH levels after stoppage indicates need for life-long therapy.

Outcome depends on the age of diagnosis and initiation of therapy, as neonatal period is crucial for neurological growth. Without treatment, these children develop as intellectually disabled and severely short-statured. With early treatment, most cases develop well, though some may be left with borderline IQ scores, poor attention span, mild hypotonia and sensorineural hearing impairment.

Subclinical hypothyroidism with TSH <10 IU/L with normal FT levels is common, specially in obese children. No treatment is required except in presence of goiter, anti-TPO antibodies or family history of hypothyroidism. However, they should be followed up cautiously and most of them revert back to normal in 3–6 months.

Juvenile hypothyroidism is defined as that presenting beyond 2 years of age. It may be congenital due to late presentation of thyroid dysgenesis/dyshormonogenesis or acquired, e.g. Hashimoto's thyroiditis or iodine deficiency, discussed later.

Hashimoto's thyroiditis (Autoimmune thyroiditis), is the commonest cause of acquired hypothyroidism and the second commonest cause of goiter in children, after endemic goiter.

Etiologically it is an autoimmune disorder with presence of various antithyroid antibodies, commonest being anti-thyroperoxidase (TPO) antibodies in 90% cases or antithyroglobulin antibodies.

Positive family history is present in 25% cases and many cases are associated with: (a) chromosomal disorders, e.g. down syndrome or turner syndrome, (b) congenital rubella syndrome, and (c) autoimmune polyglandular endocrinopathies, e.g. type I (with Addison disease and mucocutaneous candidiasis) or type II (with Addison disease and insulin dependent diabetes mellitus).

Histopathologically, AIT is characterized by lymphocytic infiltration/follicle formation, followed by atrophy and fibrosis.

Clinically, most cases present in adolescent girls (male: female ratio-1:5) with two characteristic features-growth retardation and Goiter. Functionally, these cases are euthyroid (most common), hypothyroid or rarely hyperthyroid.

Clinical features depend upon duration of hypothyroidism and include firm and nodular goiter, short stature, dry scaly skin, cold intolerance, constipation, weight gain, facial puffiness, precocious or delayed puberty, menstrual irregularities, proximal muscle weakness, calf muscle pseudohypertrophy (Kocher-Debre-Semalaigne syndrome). Later course is variable and over the years, goiter may reduce or disappear with normalization of thyroid functions

Diagnosis: While definitive diagnosis requires biopsy, following supporting features are often enough make a diagnosis of Hashimoto's thyroiditis: (a) sporadic goiter in non-endemic area, (b) elevated *anti-TPO antibody* titers, and (c) presence of other autoimmune disorders.

Treatment depends on functional status and no therapy is required for euthyroid cases. Hypothyroid cases need Eltroxin therapy to begin with lower doses 4–6 µg/kg and titrated up over 3–4 weeks. Eltroxin should be given on empty stomach in morning.

Follow-up hormonal assay is advised every 3 months for 2 years and then every 6 months, as the functional status may change from hypo-to hyper-thyroid state. Persistent nodular goiter despite thyroxin therapy for many months should be evaluated for thyroid carcinoma.

22.3.2 GOITER

Goiter is an enlargement of thyroid gland with normal or abnormal functions, i.e. euthyroid (most common), hypothyroid or hyperthyroid state.

While in euthyroid/hypothyroid states, goiter represents a compensatory mechanism to restore normal thyroid hormone activity, hyperthyroid goiters are often caused by primary tumors of gland. Clinical manifestations depend on the size of the gland (pressure symptoms) and functional state.

Etiology of Goiter is enumerated in **Table 22.7**, though some important causes are as follows:

- ***Endemic goiter*** due to iodine deficiency is the commonest cause of goiter in Indian children (Ch 22.3.3), though the incidence has declined in recent years due to universal iodination of common salt.
- ***Puberty Goiter*** is common in adolescent girls of endemic regions for Iodine deficiency due to increased physiological demand unmasking sub-clinical iodine deficiency. It is essentially euthyroid and disappears spontaneously after a few years.
- ***Congenital goiter*** is mainly caused by endemic iodine deficiency in mother or rarely due to hormonal-biosynthesis defects or exposure of fetal thyroid to goitrogens, e.g. anti-thyroid drugs in mother. Clinically, congenital goiters are usually small and asymptomatic, but large goiters may present with pressure symptoms, e.g. respiratory distress. While most cases are euthyroid, a short course (1–2 weeks) of Eltroxin therapy is indicated to suppress feedback mechanisms and reduce the gland size.
- ***Sporadic goiter:*** Hashimoto's thyroiditis is the commonest cause of sporadic goiter in older children, which is typically nodular and must be differentiated from non-nodular puberty goiter.

TABLE 22.7: Common causes of goiter

Endemic	IDDs in children
Congenital	IDDs in mother Hormonal synthesis defects Maternal use of goiterogens*
Sporadic	Hashimoto's thyroiditis Hormone synthesis defects Colloid/puberty goiter Goiterogens*

IDD: Iodine deficiency disorders
e.g. Cough syrups, antithyroid drugs, amiodarone, lithium, etc.

- ***Solitary thyroid nodules*** may be benign or malignant and need fine needle aspiration cytology to exclude malignancy, specially if they are firm, less-mobile and have associated lymphadenopathy.

22.3.3 IODINE DEFICIENCY DISORDERS

Iodine deficiency disorders (IDDs) is a common term used to describe various manifestations of dietary iodine deficiency, prevalent in certain geographical regions of India and developing world.

Epidemiology: Recommended dietary intake for iodine is ~100–150 µg/kg/day, which is adequately present in breast milk. In India, IDDs are mainly seen in sub-himalayan regions, e.g. Himachal Pradesh, northern Uttar Pradesh and Jammu and Kashmir, due to wash-out of iodine containing soil by large rivers. Reported incidence of IDDs in India varies from 10–40% in different endemic states. IDDs are relatively uncommon in coastal states due to consumption of iodine-rich sea foods.

Clinical spectrum: While endemic goiter and endemic cretinism are two well-defined manifestations of IDDs, Subtle features, e.g. short stature, mild mental retardation or learning disabilities are perhaps more common **(Table 22.8)**.

a. **Endemic goiter,** more common in girls, represents mild/moderate IDDs with compensatory enlargement of thyroid gland with variable size. In mild cases, goiter may appear only during periods of stress, e.g. puberty, pregnancy, etc. and disappear subsequently.

   WHO (1994) classifies goiter into 3 stages or grades, i.e. Stage 0: No goiter, Stage 1A: Palpable but not visible even on extended neck, Stage 1B: Palpable but visible only on extended neck, Stage 2: Visible in normal neck position and Stage 3: Very large goiter, visible from a distance.

   Most cases are clinically euthyroid, though biochemical abnormalities with raised TSH and T3 levels and low T4 levels are common. Combination of low T4/high T3 levels indicate preferential secretion or increased conversion to more bioactive T3 as a compensatory mechanism.

b. **Endemic cretinism** is the commonest cause of preventable mental retardation, seen mainly in populations with severe iodine deficiency. Two overlapping clinical variants of endemic cretinism **(Table 22.9)** are well known:
   - ***Neurological type,*** presenting with mental retardation, deaf-mutism and upper motor neuron signs, e.g. hypereflexia and Babinski sign. It is attributed to severe iodine deficiency in mother and intrauterine fetus.
   - ***Myxedematous type*** is attributed to combined intrauterine as well as postnatal iodine deficiency, presenting with stunted growth, delayed puberty and myxedema along with signs of neurological type.

TABLE 22.8: Spectrum of iodine deficiency disorders*

Endemic goiter
Mental retardation, learning disability
Hearing and speech defects
Short stature
Extrapyramidal spasticity
Endemic cretinism (hypothyroidism)
+ Intrauterine fetal death

*in increasing order of severity

TABLE 22.9: Neurological *vs* myxedematous cretinism

	Neurological	*Myxedematous*
Goiter	Present	Absent
Mental retardation	+	+
Deaf-mutism	+	+
UMN signs	+	+
Short stature	–	+
Delayed puberty	–	+
Myxedema	–	+
Thyroid function tests	Normal	Abnormal

UMN: Upper motor neuron signs

Treatment is mainly preventive. Administration of single IM injection of iodinated poppy seed oil is indicated in: (a) mothers, to prevent iodine deficiency during future pregnancies, and (b) in myxedematous children below 4 years to optimize stature, onset of puberty and cosmetic appearance. Neurological manifestations are irreversible. Surgery is needed only in cases with pressure symptoms or for cosmetic reasons.

National Iodine Deficiency Disorders Control Programme (NIDDCP)

National Iodine Deficiency Disorders Control Programme (1992), in continuation of previous National Goiter Control Programme (1962), aims to prevent, control and monitor various IDDs and bring down the incidence <10%.

Major components of NIDDCP include:

- *Continuous surveillance* of IDDs, using goiter prevalence, urinary iodine excretion or neonatal screening (TSH >5 IU/L),
- *Universal iodinization* of common salt to ensure iodine content of >15 ppm at consumption level and >30 ppm at production level. Potassium iodate is commonly used for iodination of salt in India.
- *Periodic monitoring* of iodinization quality at production as well consumption level at national reference laboratories, and
- *Information, education and communication* activities.

WHO also recommends Iodine supplementation in areas of moderate and severe iodine deficiency with Goiter rate >20%, by a single yearly dose of iodized oil-400 mg to all reproductive age, pregnant/lactating women and 200 mg to infants below two years, if not on fortified complementary feeds.

22.3.4 HYPERTHYROIDISM

Hyperthyroidism is very rare in children, almost always caused by Graves disease, though rare causes include toxic uninodular goiter (Plummer disease) or thyroid adenoma/carcinomas.

Graves' disease is clinically characterized by hyperthyroidism and ophthalmopathy, with or without other complications.

Etiologically, Graves' disease is an autoimmune disorder, associated with increased levels of thyrotropin receptor stimulating and blocking antibodies (TRsAb, TRaAb) and the balance between the two decides the course of disease. It is frequently associated with other autoimmune disorders with specific HLA types (B8, D3, DR3), e.g. Addison's disease, T1DM and myasthenia gravis. Ophthalmopathy is caused by antibodies shared between thyroid and eye muscles.

Clinically, less than 5% of cases with Graves disease are children, most common during adolescence and in females. Family history is often present. Childhood course is variable and less fulminant than in adults, presenting with:

- Failure to thrive, despite voracious appetite;
- Neurological features, e.g. emotional lability, tremors, poor attention span and school performance;
- Autonomic disturbances, e.g. tachycardia, hypertension, facial flushing, excessive sweating, etc.
- Firm, homogenous goiter, though it may be absent;
- Uncommon signs of ophthalmopathy, e.g. exophthalmos, lagophthalmos and infrequent blinking.

Thyroid crisis/storm is rare in children but may present with acute hyperthermia, severe tachycardia and rapidly developing coma. Severe or long-standing cases may also develop cardiac complications, e.g. cardiomegaly, congestive cardiac failure or arrhythmia.

Diagnosis is based on: (a) elevated FT3/FT4 levels with low TSH levels, (b) presence of TRsAb, and (c) thyroid scan showing rapid concentration of radioiodine in thyroid. Thyroid scan also helps to differentiate Graves disease (↑ uptake) from Hashimoto thyroiditis (uptake).

Management of these cases includes:

- *Antithyroid drugs*, e.g. Carbimazole or Methimazole (0.25–1.0 mg/kg/day q24hr), with doses tailored according to the response. Propylthiouracil is contraindicated in children due hepatotoxicity.
- *Radioiodine* (^{131}I) may be used as initial choice in children >10 years. Most cases become euthyroid with single dose only, though post-radiation hypothyroidism is almost inevitable.
- *Surgery* (subtotal thyroidectomy) or radioablation is the last resort in refractory cases and should be considered only after euthyroid state has been achieved by medical treatment.
- *Symptomatic therapy* with β-blockers, e.g. propranolol (0.5–2.0 mg/kg/day q8hr) is advised in cases with marked sympathetic hyperactivity.
- ***Thyroid storm*** may be treated with steroids, propranolol and antithyroid drugs along with supportive measures. Steroids inhibit peripheral conversion of T4 to T3.

Ophthalmopathy resolves with therapy though severe cases have been treated with steroids. All cases should be monitored clinically with periodic hormonal assays and TRsAb levels.

Neonatal Graves' disease is seen in ~2% babies of mothers with Graves disease due to placental transfer of TRsAb and presents with prematurity, intrauterine growth retardation, restless/irritable baby, lack of weight gain, advanced bone age and cardiovascular signs of hyperthyroidism. These cases should be treated with β-blockers and Methimazole till remission, which is common by 3–4 months of age.

22.4 PARATHYROID DISORDERS

Parathyroid glands develop from the 3rd and 4th branchial pouches and secrete Parathormone (PTH)-a polypeptide hormone with vital role in calcium metabolism along with Vitamin D and calcitonin **(Fig. 7.2)**. PTH secretion is mainly regulated by serum calcium levels though a critical magnesium concentration is also essential. Hypocalcemia increases and hypercalcemia inhibits PTH secretion.

PTH increases serum calcium levels by increasing its: (a) absorption from gut, (b) reabsorption from kidney, and (c) mobilization from bones. Renal action is mainly mediated by enhanced activity of 1-α hydroxylase enzyme, which facilitates synthesis of 1,25-dihydroxycholecalciferol-activated vit D.

PTHrP, a PTH homologue is produced in almost every cell of the body including embryonic tissues and activates PTH receptors. However, its role is more critical for maternal-fetal calcium transfer and normal fetal development.

Hypoparathyroidism, i.e. decreased PTH levels, is characterized by decreased serum calcium and elevated serum Phosphate levels, with/without clinical manifestations.

Etiology of hypoparathyroidism includes:

- Congenital parathyroid aplasia, as an isolated defect or with other malformations, e.g. DiGeorge syndrome.
- Autoimmune parathyroiditis, isolated or as a part of polyendocrinopathy type I.

- Iatrogenic injury during thyroid surgery/irradiation or hemosiderosis (multiple transfusions in thalassemia)
- End-organ resistance (pseudohypoparathyroidism), as discussed later.

Transient hypoparathyroidism is common in newborns of mothers with hyperparathyroidism and may present with neonatal tetany.

Clinical presentation may vary from: (a) asymptomatic hypocalcemia, to (b) early signs—muscle pain/cramps and paresthesia, (c) latent or manifest tetany, (d) recurrent seizures, or (e) chronic disease with dental abnormalities, cataract, growth/developmental retardation and mucocutaneous candidiasis.

Diagnosis depends on:

- Hypocalcemia with hyperphosphatemia, with normal, low or even high alkaline phosphatase levels,
- Decreased PTH levels on immunometric assay,

Radiological abnormalities, e.g. metaphyseal hyperdensity in long bones and basal ganglia calcification on CT scan are present in ~ 50% cases.

Management of these cases include:

a. *Emergency treatment* of seizures/hypocalcemia with IV calcium 10% (1–2 ml/kg 6-hourly) along with IV/PO Calcitriol 0.25 µg stat followed by 0.01–0.1 µg/kg 12-hourly for 3–4 days, till serum calcium returns to normal. (Calcitriol is active Vitamin D, i.e. 1,25 (OH)2 D3)
b. *Long-term control* with PO Calcitriol 20 to 60 ng/kg/day and calcium 30 to 75 mg/kg/day, along with reduced intake of high phosphorus diet, i.e. milk, egg, etc.

DiGeorge syndrome is an important cause of congenital hypoparathyroidism with abnormal development of III and IV pharyngeal pouches due to microdeletion in chromosome 22 (22q11.2) and often associated with thymic aplasia, persistent hypocalcemia, facial dysmorphism and cardiac defects.

Pseudohypoparathyroidism (Albright hereditary osteodystrophy) is characterized by genetically determined decreased responsiveness of PTH receptors, leading to hypocalcemia despite raised PTH levels (d/d true hypoparathyroidism). Most cases present at 7–8 years of age with recurrent tetany and typical somatic features, e.g. brachydactyly with dimpled dorsum of hand and short 4th metacarpal. Mental retardation, short stature, cataract and basal ganglia calcifications are common.

Hyperparathyroidism, i.e. increased PTH secretion may be primary (parathyroid disease) or secondary (to hypocalcemia due to any cause), the later being inconsequential due to absence of hypercalcemia.

Etiology: Primary hyperparathyroidism is almost always caused by parathyroid tumors, e.g. solitary adenoma or multiple endocrinal neoplasia (type I), except rare cases of ectopic PTH-secreting tumors or neonatal parathyroid hyperplasia.

Clinically, Primary hyperparathyroidism presents with:

- Early hypercalcemia with weight loss, muscular weakness, constipation and polyuria/polydipsia
- Prolonged calciuria leading to nephrocalcinosis, renal calculi and chronic renal failure.
- Increased bone resorption, leading to backache, limb pains, deformities and pathological fractures.
- PTH crisis (S. Ca^{++} >15 mg/dl) presenting as rapidly progressive oliguria and renal failure.

Diagnosis rests on:

- Elevated PTH levels with hypercalcemia.
- X-rays showing typical subperiosteal resorption of bone (in phalanges) apart from rarefaction/trabeculation/cystic changes in skull and renal calculi/nephrocalcinosis in abdomen.
- Abnormal renal functions with hyposthenuria.
- *D/D:* Primary hyperparathyroidism must be distinguished from other causes of hypercalcemia (Ch 7.4) and secondary hyperparathyroidism (with normal/low calcium levels).

Management of primary hyperparathyroidism is essentially the surgical removal of tumor, followed by calcium and Calcitriol supplementation and correction of deformities.

22.5 ADRENAL DISORDERS

Adrenal gland is made up of the cortex and medulla, each functioning as a separate endocrine unit.

Adrenal cortex is functionally divided into three zones-outer zona glomerulosa, middle zona fasciculata, and inner zona reticularis to produce different hormones-glucocorticoids (cortisol), mineralocorticoids (aldosterone), and sex steroids.

Glucocorticoids, e.g. cortisol (most potent natural glucocorticoid) are produced in zona fasciculata, under control of pituitary ACTH, which in turn is regulated by hypothalamic CRH.

Mineralocorticoid, i.e. aldosterone, is synthesized in zona glomerulosa. mainly regulated by Renin-angiotensin system.

Sex-steroids, e.g. androgens and small quantities of estrogens are produced in zona fasciculata and zona reticularis as well as in gonads. Adrenals are main source of sex-steroids in pre-pubertal period, while there is sudden surge of gonadal steroid production at the onset of puberty. Exact physiology of sex-steroid secretions is complex, discussed in Ch 22.6.2.

All adrenocortical hormones are derived from cholesterol via different but inter-related enzymatic pathways **(Fig. 22.2)**. Enzymatic block in one pathway leads to—(a) accumulation of proximal metabolite with or without biological activity, (b) deficiency of end-hormone, i.e. cortisol, aldosterone or androgens, and (c) diversion

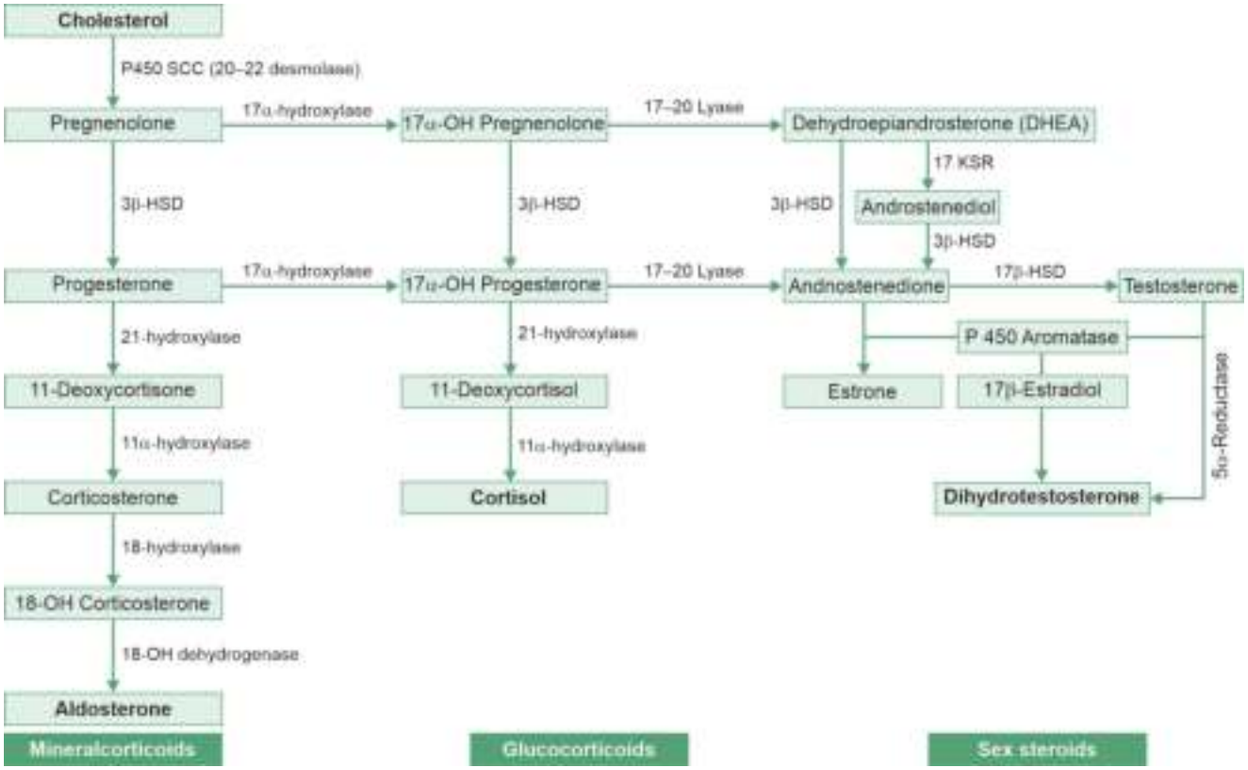

Fig. 22.2: Adrenal steroidogenesis.

HSD: Hydroxysteroid dehydrogenase; **KSR:** Ketosteroid reductase

of intermediate substrate to produce other hormones, leading to their excess.

Adrenal medulla, though structurally a part of adrenal, has totally unrelated biological function, i.e. secretion of direct-acting sympathetic catecholamines, e.g. norepinephrine, epinephrine and dopamine. Its functions are neither related to adrenal cortex, nor regulated by hypothalamo-hypophyseal axis. Pheochromocytoma is the principle disorder of adrenal medulla, discussed later.

22.5.1 ADRENOCORTICAL INSUFFICIENCY

Adrenocortical insufficiency, i.e. impaired secretion of adrenocortical hormones, may be *primary* (adrenal disorders) or *secondary*, due to pituitary ACTH or hypothalamic CRH deficiency. While primary insufficiency is associated with decreased secretion of all adrenocortical hormones, secondary adrenal insufficiency has no evidence of mineralocorticoid deficiency, which is regulated by the renin-angiotensin mechanism.

Adrenocortical deficiency results from many congenital/acquired lesions of the hypothalamus, pituitary or adrenals **(Table 22.10)**. Congenital adrenal hyperplasia (Ch 22.5.2) or adrenal hemorrhage in septic/asphyxiated newborns is the commonest cause of primary adrenal insufficiency in infancy, while older cases are usually due to Addison disease (Ch 22.5.3) or acute adrenal insufficiency in severe infections, e.g. meningococcemia (Waterhouse-Friderichsen syndrome).

Secondary adrenal insufficiency is usually seen after sudden withdrawal of steroids after prolonged therapy, due to suppression of the hypothalamo-pituitary axis.

TABLE 22.10: Causes of adrenal insufficiency

Secondary *(Pituitary/Hypothalamic lesions)*
- ***Congenital***
  - Isolated CRH/ACTH deficiency (Genetic)
  - Pituitary aplasia/hypoplasia
- ***Acquired***
  - Intracranial infections/trauma/surgery
  - Pituitary/hypothalamic tumors
  - *Iatrogenic:* Sudden steroid withdrawal

Primary *(Adrenal defects)*
- ***Congenital***
  - Adrenal aplasia/hypoplasia
  - Isolated cortisol/aldosterone deficiency
  - *Hormonal synthesis defects:* CAH
  - Adrenoleukodystrophy
  - *End-organ resistance:* Pseudohypoaldosteronism
- ***Acquired***
  - *Addison disease:* Autoimmune, tuberculosis
  - *Infection:* Waterhouse-Friderichsen syndrome
- ***Iatrogenic***
  - *Drugs:* Ketoconazole, anticonvulsants
  - Adrenectomy

22.5.2 CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia (CAH) is a group of inherited autosomal recessive disorders, characterized by deficiency of any one of the five enzymes involved in cortisol production from cholesterol, **(Fig. 22.2)** the commonest being 21-hydroxylase deficiency in >90% cases, discussed here.

21-hydroxylase deficiency blocks the formation of mineralocorticoids and glucocorticoids and leads to excess production of androgenic steroids (DHEA, DHEAS and androstenedione) and testosterone. Several mutations involving gene CYP21 on chromosome 6p21.3 are responsible for CAH.

Clinical features depend on severity of enzyme deficiency, ranging from salt-losing variety with complete absence of enzyme) to the non-salt losers with partial enzyme deficiency.

Clinically, these cases are classified as—(a) salt-wasting type presenting in infancy, (b) simple virilizing type presenting in infancy or childhood, and (c) non-classic CAH, presenting in adolescents or adults.

Salt-wasting CAH is associated with complete enzyme deficiency and presents in infancy with:

- Virilization in females at birth, with variable severity ranging from mild clitoral hypertrophy to labial fusion and even complete masculinisation **(Fig. 22.5)**. Virilizing effect in males is not that obvious and present later with hyperpigmentation of the body, nipples, umbilicus and genitals.
- Signs of salt-losing are present since neonatal period in 75% cases and include-failure to thrive, polyuria, recurrent vomiting and sepsis-like features with negative sepsis screen. Adrenal crisis with hypotension and shock is common in severe cases. Symptoms may not manifest till serum sodium falls <125 mEq/L.
- Hypertension is characteristically absent in this enzymatic variety of CAH.

Simple virilizing form with partial enzyme deficiency presents only with virilization in girls and precocious puberty in boys, with no signs of salt-losing.

Non-classical forms, also due to partial enzyme deficiency, present with very mild features of hyperandrogenism, e.g. hirsutism, acne and menstrual irregularities.

Diagnosis must be suspected in any infant with virilization or ambiguous genitals with/without features of salt-loosing. History of consanguinity, similar illness in siblings or unexplained deaths in previous newborns with vomiting are important diagnostic clues. Laboratory diagnosis depends on:

- *Elevated Serum 17-hydroxy progesterone (17-OHP) levels* > 200 ng/dl. These levels depend on the severity of enzyme deficiency, being as high as >10000 ng/dl in salt-wasting CAH.
- *ACTH challenge test*, showing 2–3 fold rise in 17-OHP levels without rise in cortisol levels, after 60 minutes of ACTH administration (IM 0.25 mg).

Serum cortisol levels are normal or reduced, with elevated ACTH, androstenedione and testosterone levels. USG reveals female structures in 46 XX individuals with virilisation.

Biochemical indicators of salt-loosing include hyponatremia, hyperkalemia, increased urinary sodium, increased plasma renin activity and low aldosterone levels.

D/D includes other causes of virilization, e.g. adrenocortical tumors, as well as rare enzymatic defects in CAH, discussed later.

Management of CAH includes:

- Life-long glucocorticoid therapy to replace the deficient cortisol and suppress overproduction of ACTH. Oral hydrocortisone (15–20 mg/m^2/day q8hr) is preferred. Higher doses (double or triple the maintenance dose) are necessary during stress, e.g. infection and surgery.
- Salt-wasting type also requires mineralocorticoid therapy with fluorohydrocortisone (PO 0.05–0.3 mg/day q12hr) and oral sodium supplements in infancy.
- Assigning the sex of rearing is important at birth to avoid later complications. Females should be reared as females irrespective of the degree of virilization, as they have normal internal genitalia, normal onset of puberty and normal fertility. Surgical correction of genital abnormalities and psychological counseling is required in cases with delayed diagnosis or wrong sex-assignment.

  Males do not suffer from wrong gender assignment but have problems of precocious pseudopuberty as well as accelerated physical and skeletal maturation.

Prenatal diagnosis is possible by chorionic villus sampling or amniocentesis to detect CYP21 mutations. High-risk mothers should be initiated on Dexamethasone (PO 20 µg/kg/day q8–12hr) from 6–8 weeks of gestation to prevent fetal virilisation and continued throughout pregnancy after confirmation of prenatal diagnosis.

Neonatal screening by estimation of 17-OHP on a dried blood sample (DBS) is possible and carried out at many centers.

Rare but important enzymatic variants of CAH include:

- **11-β-hydroxylase deficiency** (5–8%) characterized by presence of hypertension and persistent hypokalemia, along with virilization. Salt wasting is uncommon.
- **3-β-hydroxysteroid dehydrogenase deficiency,** characterized by mild virilization, clitoromegaly and menstrual irregularities in girls or ambiguous genitalia in boys.

22.5.3 ADDISON DISEASE

Addison disease denotes primary adrenal insufficiency of acquired etiology with gradual destruction of the adrenal cortex, while medulla is usually preserved.

Etiology: Autoimmune destruction of the adrenal glands is the commonest cause of Addison disease with frequent presence of autoantibodies against 21-hydroxylase enzyme. Addison disease as a part of autoimmune polyendocrinopathy syndromes is rare in childhood.

Other causes include infections, e.g. tuberculosis and meningococcemia, drugs, e.g. ketoconazole and adrenal hemorrhage in sepsis, asphyxia or bleeding disorders. Waterhouse-Friderichsen syndrome denotes acute adrenal insufficiency following adrenal hemorrhage in meningococcemia.

Clinical presentation may be acute or insidious, depending on the etiology and severity/rapidity of acquired disease.

a. ***Chronic progressive adrenal insufficiency*** (Addison disease) usually presents in older children with:

- Signs of glucocorticoid deficiency, e.g. recurrent hypoglycemia, vomiting, abdominal pain and failure to thrive.
- Signs of mineralocorticoid deficiency, e.g. salt craving, hypotension and muscular weakness.
- Signs of androgen deficiency, e.g. poor development of secondary sexual characteristics.
- Signs of compensatory ACTH excess, e.g. hyperpigmentation of skin.

While all adrenocortical functions are lost in advanced disease, early cases may present with isolated cortisol deficiency.

b. ***Acute adrenal insufficiency (Adrenal crisis)*** is a life-threatening emergency, seen in septic/asphyxiated newborns, meningococcemia or acute stress states, e.g. infections, surgery, etc. These cases present with sudden vomiting, hypoglycemia, hypotension/shock and intractable biochemical abnormalities, e.g. hyponatremia, hyperkalemia, etc.

D/D: Addison disease must be differentiated from other causes of adrenal insufficiency including genetic defects, e.g. CAH or adrenal hypoplasia congenital (DAX1 gene mutation) or secondary adrenal insufficiency due to pituitary or hypothalamic causes.

Diagnosis is based on:

- Low resting cortisol levels (<5 µg/dl) which do not rise on ACTH stimulation test, i.e. measuring cortisol levels before and 30 or 60 minutes after 250 µg of cosyntropin (ACTH) by rapid intravenous infusion or Intramuscular injection. Normal resting levels that do not increase after administration of ACTH indicate absence of adrenocortical reserve, while low initial level followed by a significant response to ACTH indicate secondary adrenal insufficiency.
- Altered plasma ACTH levels to differentiate primary (↓ACTH) from secondary (↓ACTH) adrenal insufficiency. Basal levels should be confirmed by stimulation tests.
- Tests for etiological diagnosis, e.g. CT/MRI of brain and abdomen, measurement of circulating antibodies in Addison disease and TB etiology.
- Other relevant tests for pituitary dysfunction in secondary disease.

Management: Acute adrenal crisis is a medical emergency, which requires intensively monitored fluid and electrolyte therapy along with IV hydrocortisone 50 mg/m^2 immediately followed by 100 mg/m^2/day in four divided doses. After the child is stable, life-long hormone replacement therapy is required as follows. as follows.

Chronic adrenal insufficiency or cases of acute adrenal crisis after recovery need life-long glucocorticoids (PO Hydrocortisone 10–12 mg/m^2/dose q8hr) in minimum possible doses, which should be stepped-up during intercurrent infections or surgery. Mineralocorticoid (PO Fluorohydrocortisone 0.05–0.3 mg/day) is necessary only in cases with aldosterone deficiency.

22.5.4 CUSHING SYNDROME

Cushing syndrome is the commonest disorder of adrenocortical hyperfunction, characterized by cortisol excess and consequent clinical features, e.g. obesity, growth failure and hypertension, etc.

Etiology: Cushing syndrome is caused by excess endogenous production of cortisol in adrenal, pituitary or hypothalamic disorders or rarely from ectopic sources, e.g. tumors **(Table 22.11)**. A functioning malignant tumor of adrenal cortex (rarely adenoma) is the commonest cause of Cushing syndrome in infancy and early childhood, while *Cushing disease*, i.e. bilateral adrenal hyperplasia, due to excessive ACTH secretion from pituitary adenoma, is more common in older cases > 6 years.

TABLE 22.11: Causes of Cushing syndrome

- Primary adrenal disease
  - Tumors, e.g. carcinoma, adenoma (>45%)
  - Primary nodular dysplasia
  - McCune-Albright syndrome
- Pituitary adenoma (*Cushing disease*) (50%)
- Hypothalamic tumors (↑CRH)
- Ectopic ACTH-secreting tumors*
- End-organ resistance
- Iatrogenic steroids (*cushingoid syndrome*)

*malignant tumors of bronchus, thymus, pancreas

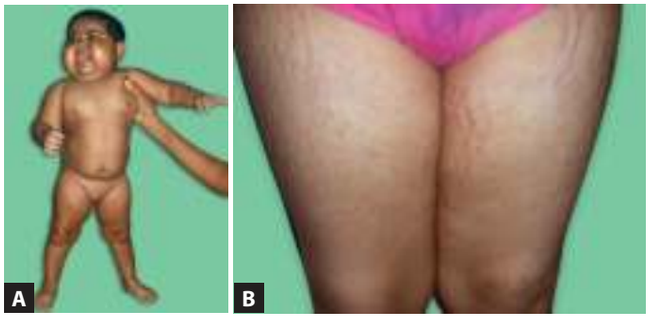

Fig. 22.3A and B: **Cushing syndrome: (A) Moon face with Hirsutism; (B) Purple striae over thighs.**

Clinical features are similar irrespective of etiology and include:

- *Truncal obesity* with buffalo hump and thin extremities due to centripetal fat distribution. Purple striae may be present on protuberant abdomen and thighs, due to skin stretching.
- *Short stature* with normal or advanced bone age (due to androgen excess).
- *Moon-like facies*, with cheek flushing, double chin and hypertrichosis **(Fig. 22.3)**
- *Masculinizing features* due to androgen excess, e.g. hypertrichosis, acne, pubic hair, deepening of voice and clitoromegaly.
- *Hypertension* is common and may lead to heart failure.
- *Other features* include easy bruising and susceptibility to infections as well as osteoporosis, psychological disturbances and proximal myopathy in long-standing cases.

Laboratory diagnosis aims to demonstrate hypercortisolism and its etiology.

- Indirect evidences of hypercortisolism include presence of polycythemia, lymphopenia, eosinopenia, hyperlipidemia, hypercalciuria, hyperinsulinemia and hyperglycemia.
- Endocrinal evaluation requires multiple tests as follows, since no single test is confirmatory.
  - *Elevated mid-night cortisol levels* (>4.4 µg/dl) strongly indicate possibility of Cushing syndrome. Midnight sample is necessary to account for diurnal variation in cortisol levels, which are highest in morning and lowest at midnight. Late-night salivary cortisol levels may be used for outdoor evaluation.
  - *Elevated 24-hr urinary free cortisol* (UFC) levels (>75 µg/m^2) is a useful screening test.
  - *Dexamethasone suppression test:* Single dose of dexamethasone (PO 25–30 µg/kg) at 11 pm normally suppresses plasma cortisol levels < 5 µg/dl at 8 AM next morning. Lack of this suppression indicates Cushing syndrome.

D/D between Cushing syndrome (adrenal) and Cushing disease (pituitary) involves:

- Low *Plasma ACTH levels* (<5 pg/ml) in adrenal tumors, which do not rise after CRH challenge (IV 1 µg/kg), unlike normal or high values in ACTH-secreting pituitary or ectopic adenomas (>15 pg/ml). Ectopic ACTH secretion must be suspected in presence of very high ACTH levels > 100 pg/ml.
- *Two-step Dexamethasone suppression test* with PO Dexamethasone for 2 consecutive days in different doses (30 µg/kg/day q6hr on day 1 and 120 µg/kg/d q6hr on day 2). Children with ACTH-independent Cushing syndrome do not show cortisol suppression. However in Cushing disease due to microadenoma of pituitary, cortisol levels are suppressed with higher doses.

In brief, Cushing syndrome due to:

- Adrenal lesions have low ACTH, high UFC and negative high-dose DST (No suppression).
- Pituitary lesions have high ACTH, high UFC and variable results on high-dose DST
- Ectopic ACTH have high ACTH, high UFC and negative high-dose DST
- Exogenous causes have low ACTH, high UFC and negative high-dose DST

Radio-imaging studies (CT/MRI) may be necessary to detect adrenal and pituitary tumors, while other X-rays may be used to detect osteoporosis and advanced bone age.

Management depends on the etiology:

- *Adrenal tumors* require unilateral or subtotal adrenalectomy, along with pre-/post-operative hydrocortisone supplementation.
- *Pituitary tumors* with adrenal hyperplasia (Cushing disease) is best treated with trans-sphenoidal microsurgery.
- *Medical therapy* with inhibitors of steroidogenesis, e.g. cyproheptadine, bromocriptine, ketoconazole, etc. is rarely effective, with frequent side effects.

22.5.5 HYPERALDOSTERONISM

Aldosterone is produced by zona glomerulosa in response to hyponatremia and hypovolemia, regulated by the renin-angiotensin system, and acts on renal tubules to increase sodium reabsorption. Hyperaldosteronism can be primary or secondary.

Primary hyperaldosteronism is rare in childhood, caused by: (a) adenoma, (b) adrenal nodular hyperplasia or (c) congenital adrenal hyperplasia.

Clinically, it present with: (a) signs of sodium retention and hypernatremia, e.g. hypertension and polyuria, and (b) signs of excess potassium excretion and hypokalemia, e.g. muscular weakness, paresthesia alkalosis, etc. Oedema is absent in primary hyperaldosteronism due to aldosterone escape phenomenon wherein atrial natriuretic peptide causes natriuresis, preventing sodium retention and oedema.

Diagnosis is supported by typical biochemical abnormalities (hypokalemia, hypernatremia, alkalosis) and confirmed by high aldosterone levels and suppressed plasma renin activity. CT/MRI helps to localize the tumor.

Treatment is mainly surgical with excision of tumor or adrenalectomy, though nodular hyperplasia may be managed with mineralocorticoid antagonists, e.g. spironolactone.

Secondary hyperaldosteronism is generally transient, caused by high renin secretion, either as: (a) compensatory mechanism to restore glomerular filtration rate, e.g. in CCF, nephrotic syndrome, renal artery stenosis, etc. or (b) due to a Renin-secreting Wilms' tumor. These cases predominantly present with features of primary disease. Hypokalemia and hypertension are absent in secondary hyperaldosteronism.

22.5.6 ADRENAL SEX-STEROID PRODUCING TUMOURS (ADRENOGENITAL SYNDROME)

Adrenal sex steroid producing tumors are rare in childhood and may be virilizing (androgen-producing) or feminizing (estrogen-producing).

- ***Androgen-producing tumors*** are usually malignant, presenting at any age with virilization in girls and precocious puberty in boys, along with accelerated linear growth and skeletal maturation. Cushing syndrome may be present in some cases.
- ***Estrogen-producing tumors*** are extremely rare and usually benign, presenting with heterosexual precocious puberty or gynecomastia in boys and peripheral precocious puberty in girls.

Diagnosis rests on elevated 24-hour urinary 17-ketosteroids and serum androgen/estrogen levels, along with abdominal CT/MRI to localize the tumor. Adrenal calcifications may be present.

Treatment is mainly surgical to enucleate the tumor with/without chemotherapy and radiotherapy.

22.5.7 PHEOCHROMOCYTOMA

Principle hormones of adrenal medulla are physiologically active catecholamines, e.g. norepinephrine, epinephrine and dopamine. Metabolites of them are excreted in urine as Vanillylmandelic acid (VMA), normetanephrine and metanephrine.

Pheochromocytoma is catecholamine-secreting tumors, arising from chromaffin cells-present in adrenal medulla or elsewhere along the sympathetic chain. Only 5–10% of all cases are encountered in children, usually in late adolescence.

Pheochromocytomas may be hereditary (AD), frequently associated with other syndromes/tumors like neurofibromatosis, etc.

Clinically these tumors present with features of catecholamine excess, i.e. (a) hypertension of variable severity, including hypertensive encephalopathy, and (b) severe cachexia despite good appetite, due to hypercatabolic state.

Diagnosis rests on elevated plasma/urinary catecholamines and their derivatives with total urinary catecholamine excretion being >300 g/24 hour. Fractionated plasma and urinary metanephrines are more useful for diagnosis as catecholamines are secreted episodically whereas metanephrines are continuously produced by tumour cells.

Urinary VMA levels may be falsely elevated after consumption of vanila-containing foods before the test and hence no longer routinely used.

Tumor may be localized by USG, CT/MRI or ^{131}I-metaiodobenzylguanidine (MIBG) scans.

Treatment is surgical removal of the tumor with preoperative α-and β-adrenergic blocker therapy, to prevent sudden adrenergic crisis due to tumor spillover and post-operative monitoring for the same.

22.6 DISORDERS OF SEX-STEROIDS

Development of gonads and external genitals is a complex interplay of various hormones, secreted from pituitary (gonadotropins), adrenals (androgens) and gonads themselves, together termed as sex-steroids. In fetal life, placenta is another site for sex-steroids secretions-estrone, estradiol and estriol (chorionic gonadotropins), utilizing fetal and maternal androgens.

Some important hormones, which play important role in gonadal disorders are as follows:

Androgens: DHEAS (Dehydroepiandrosterone sulfate) is the predominant adrenal androgen in circulation, derived from adrenals directly or converted from peripheral sulfation of another adrenal androgen-DHEA. DHEAS levels are low in childhood but begin to rise before other hormonal changes at puberty to promote growth as well as secondary sexual characteristics, e.g. pubic/axillary hairs.

Testicular hormones: Testosterone is the main hormonal product of testis, secreted by Leydig cells from 8–12 weeks of gestation onwards and responsible for initial virilization of fetus. After initial virilization, testosterone level drop and remain low till onset of puberty when it increases again to cause testicular and penile growth, typical body odor and voice changes. Within target cells, some testosterone is converted into other derivatives, e.g. dihydrotestosterone and estradiol.

Other important testicular hormones include Müllerian-inhibiting substance (MIS) that causes involution of fetal mullerian ducts, inhibin-B and Follistatin that inhibit pituitary FSH secretions, and many other growth factors.

Ovarian hormones: Estrogens (estradiol, estrone and estriol) and progesterone are predominant hormones of ovary, though also produced by adrenals as well as testis. These hormones are critical for menstruation and development of breasts, as well as to exert a negative feedback on pituitary gonadotropins.

Other important ovarian hormones include inhibins, activins (diamers of inhibin, to promote FSH secretion) and many other growth factors.

Gonadotropins from pituitary, i.e. LH and FSH, are critical for onset of puberty as well as ovogenesis and menstrual changes in females.

Clinically, disorders of sex steroids may present at birth with ambiguous genitalia or later as delayed/precocious puberty, gynecomastia, amenorrhea/sterility, etc. discussed in this chapter.

22.6.1 DISORDERS OF SEX DEVELOPMENT (AMBIGUOUS GENITALIA)

Disorders of sex development (DSD) are a group of congenital conditions wherein either chromosomal, gonadal or anatomical sex development is atypical. Previous terminologies like ambiguous genitalia, intersex, pseudohermaphrodite are now avoided as they are non-informative and stigmatizing.

Physiology of sex differentiation may be divided into three components-determination of: (a) genetic or chromosomal sex, (b) gonadal sex, and (c) genital sex or phenotype **(Fig. 22.4)**.

a. **Genetic sex** is determined at conception, by chance selection of the sex chromosomes in zygote—XX pair develops as potential future female and XY pair develops as potential future male.

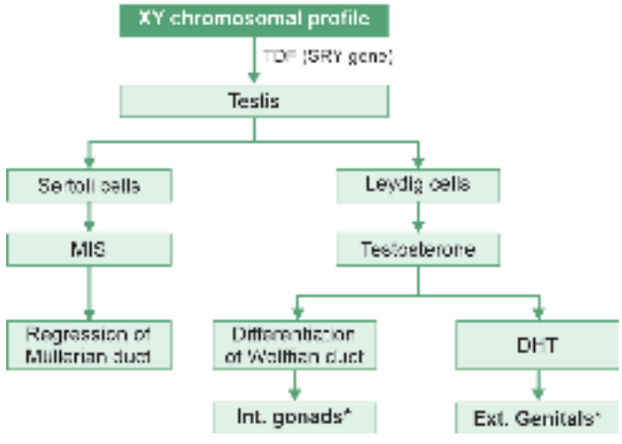

Fig. 22.4: Determination of male sex and differentiation
Absence of Y chromosome, i.e. SRY gene leads to failure of above steps and development of female fetus.
*epididymis, vas deferens, seminal vesicles. **penis, scrotum, prostate
DHT: Dihydrotestosterone; **MIS:** Müllerian-inhibiting substance; **TDF:** Testicular determining factor

b. **Gonadal sex** is determined at the end of 6th gestational week, by the presence/absence of a SRY gene on short arm of Y chromosome. Till then, fetal gonads are bipotential, capable of developing as both-the ovary or the testis. At 42nd day of gestation, the genital ridge of the XY fetus differentiates as testes in presence of SRY gene and as ovaries in its absence. Thus, presence/absence of SRY gene is one of the critical determinants of gonadal sex of fetus.

c. **Internal genital sex** differentiates after 8th week. Till then, both primitive sexual ducts, i.e. müllerian and Wolffian structures are present. This differentiation depends on presence/absence of male gonad, i.e. testis and not on ovaries.

In males, developing testes secrete:

- Anti-Mullerian hormone (AMH) from Sertoli cells, which leads to regression of Müllerian ducts.
- Testosterone from Leydig cells, which stimulates stabilization and differentiation of Wolffian ducts into the male internal genitals, i.e. epididymis, vas deferens, seminal vesicles.

In females, absence of testicular hormones permits development of female internal genitals with:

- Atrophy of Wolffian ducts due to the absence of testosterone, and
- Persistence of Müllerian structures in absence of AMH, to develop as upper vagina, uterus and fallopian tubes.

Development of wolffian ducts and regression of Müllerian ducts on each side depends on ipsilateral production of testosterone and MIS respectively. Hence, gonadal elements on the side determine ipsilateral internal genitalia. A streak gonad, which doesn't produce testosterone or MIS leads to development of poorly formed Müllerian structures, e.g. hypoplastic uterus on the side of streak gonad.

d. **External genitals** develop at 9th–13th week, depending on dihydrotestosterone (DHT)-a potent androgen, produced by conversion of testosterone in presence of 5 -reductase enzyme.

- *In males*, presence of DHT leads to virilization of penis and scrotum, elongation of urethra and development of prostate. Development of fetal penis is also influenced by placental human chorionic gonadotropins.
- *In females*, absence of testicular androgens leads to differentiation of external genitalia as females.

Types: While older classifications were based on clinical patterns, presently DSDs are classified as-(a) sex chromosomal DSD, (b) 46XY DSD, c) 46XX DSD.

a. ***Sex chromosomal DSD,*** (Previously, true hermaphrodites) denote numerical abnormalities of sex chromosomes (eg. 45X, 47XXY and mosaicisms)

TABLE 22.12 Disorders of sex development

I. Sex chromosomal DSD
- 45 X (Turner syndrome/variants)
- 47 XXY (Klinefelter syndrome variants)
- 46XX, 46XY, 45 X/46XY (Mixed gonadal dysgenesis)

II. 46 XY DSD

Disorders of testicular development:
- Complete/partial gonadal dysgenesis
- Testicular regression
- Ovotesticular DSD

Disorders of androgen production:
- Congenital adrenal hyperplasia[1]
- Androgen biosynthesis defects[2]
- *Syndromic:* Smith-Lemli-Opitz Syndrome

Disorders of androgen action:
- Complete/partial androgen insensitivity

Unclassified:
- Hypospadias/Epispadias
- Persistent Mullerian duct syndrome

III. 46 XX DSD

Disorders of ovarian development:
- Monogenic forms
- Ovotesticular DSD

Disorders causing androgen excess:
- Congenital adrenal hyperplasia[3]
- Aromatase deficiency
- Iatrogenic (maternal androgen use)
- Virilizing ovarian or adrenal tumours

Unclassified:
- Mayer-Rokitansky syndrome

[1]STAR, 3 beta HSD, 17 alpha hydroxylase deficiencies
[2]17 beta HSD, 5 alpha reductase deficiencies
[3]21 hydroxylase, 11 beta hydroxylase, 3 beta HSD deficiencies

b. ***46 XX DSD:*** (previously female pseudohermaphroditism) denote partial or complete virilization of external genitals with internal gonads as ovaries/ovotestes with genetic sex of XX type.

c. ***46 XY DSD*** (previously male pseudohermaphroditism) denote undervirilized or female-like external genitals with internal gonads as testes/ ovotestes and genetic sex of XY type.

Etiological classification of DSDs has been depicted in **Table 22.12**, though CAH and androgen insensitivity are commonest causes of 46XX DSD and 46 XY DSD respectively.

Diagnostic evaluation of these cases includes:

a. **Careful family history** (androgen insensitivity syndrome, CAH), previous obstetrical history of fetal, neonatal loss (salt-losing CAH) or maternal drug ingestion (estrogen/progesterone) during pregnancy.

b. **External genital appearance** in DSDs covers a spectrum from normal female (severe undervirilization) to genital ambiguity to normal male (severe virilization). Hyperpigmentation could be a pointer to CAH. Normal looking female genitalia with inguinal gonads may be a case of androgen insensitivity syndrome, while normal looking male genitalia with undescended testis and empty scrotum may actually be a virilized female with CAH **(Fig. 22.5)**.

Fig. 22.5: Ambiguous genitalia.

In ambiguous appearing genitalia it is better to use neutral terms like genital tubercle (instead of penis/clitoris), labioscrotal folds (instead of labia or scrotum), gonads (instead of ovaries/testes). Palpation of missing testes in inguinal canal is essential to arrive at a preliminary diagnosis, before investigations.

c. **Investigations** in all cases include:
- ***Determination of genetic sex*** by karyotyping. Rapid tests such as Y chromosome PCR for SRY gene are increasingly popular, as karyotyping may take weeks.
- ***Determination of internal gonads*** and genital structures by abdominal/pelvic sonography or laparoscopy. Very small/undescended testis may be also identified by HCG stimulation test.
- ***Relevant etiological investigations,*** dictated by clinical impression, e.g.:
  - Bone-age determination (advanced in CAH, delayed in aromatase deficiency),
  - USG/CT/MRI for central/gonadal tumors.
  - Chromosomal studies for Y-specific DNA sequence (Turner/Klinefelter syndrome)
  - Hormonal assays, e.g. testosterone/DHT ratio (5 -reductase deficiency), DHEA, cortisol and 17-OHP levels for adrenal functions, gonadotropin levels (elevated in androgen resistance)
  - Biochemical tests for hypoglycemia or electrolyte abnormalities (in CAH)

Gonadal biopsy is indicated only in suspected cases of gonadal dysgenesis/ovotesticular DSD, which is very rare. Important differentiating features of various causes of DSD are summarized in **Table 22.13**.

TABLE 22.13: Important D/D of ambiguous genitalia

Type/Cause	*External gonads*	*Mullerian structures**	*17-OHP*
46XY DSD			
Androgen insensitivity syndrome	Variable	Absent	Normal
Testicular differentiation defect	Variable	Partial	Normal
Androgen biosynthetic defects	Variable	Absent	Normal
46XX DSD			
Cong. adrenal hyperplasia	No	Present	Elevated
Non-adrenal	No	Present	Normal
Sex chromosomal DSS			
Ovotesticular DSD	Variable	Partial	Normal

*On USG

Management: Important issues in management of these cases are—(a) assignment of sex of rearing, (b) treatment of primary cause, e.g. CAH, if possible, (c) psychological support/counseling, and (d) reconstruction of external genitals and other defects, e.g. hypospadias. Removal of non-functioning gonads, especially in gonadal dysgenesis is advisable to avoid later risk of tumors.

Assignment of sex of rearing depends upon the underlying disorder and the gender identification of the individual though as a general rule:

- All 46XX should be reared as females, even if highly virilized.
- Fully/significantly feminized 46XY (such as in complete androgen insensitivity) should also be reared as females, if cause is not treatable. Estrogen replacement should be started at pubertal age for breast development in cases reared as females.
- 46XY with mild feminization or treatable cause must be reared as males.

Micropenis, a common feature in ambiguous genitalia, denotes stretched penile length of <2.5 cm in newborn or < 2SD for baby's age in older children without associated hypospadias.

Common causes of micropenis include: (a) *hypothalamic-pituitary disorders*, e.g. Kallmann syndrome, hypopituitarism, Prader-Willi syndrome, and (b) *testicular disorders*, e.g. Klinefelter syndrome, rudimentary testis or testicular regression.

In selected children, stimulation with testosterone can be used to facilitate phallic growth. Gender reassignment will be necessary in severe case or those who fail to respond to testosterone therapy.

22.6.2 DISORDERS OF PUBERTY

Puberty is the most important component of adolescent growth, characterized by appearance of secondary sexual characteristics as well as maturation of reproductive functions, e.g. menstruation. Average age for the onset of puberty in Indian children is ~11 years in females and ~11.5 years in males.

Important pubertal changes in girls include: (a) thelarche, i.e. breast enlargement, (b) adrenarche, i.e. appearance of pubic hair, and (c) menarche, i.e. onset of menstruation.

Corresponding changes in boys include: (a) increase in testicular size, (b) adrenarche, and (c) penile enlargement.

Physiology of puberty: Onset and progression of puberty is regulated by many hormonal changes in HPG (hypothalamic-pituitary-gonadal) axis involving: (a) hypothalamic GnRH, (b) pituitary gonadotropins, e.g. LH and FSH, (c) gonadal steroids, e.g. estrogens and testosterone, along with adrenal androgens, e.g. DHEA/DHEAS **(Fig 22.6)**, in following general sequence:

- ***Pre-pubertal hyothalamic hypersensitivity:*** During pre-pubertal stage, gonadal steroid production is negligible but hypothalamus is extremely sensitive to them and even miniscule hormone levels are enough to exert negative feedback on hypothalamic GnRH and pituitary gonadotropin secretion.
- ***Earliest hormonal change*** to herald the onset of puberty is increase in adrenocortical androgen production (DHEA, DHEAS) at ~6–8 years, initiating adrenache, i.e. development of pubic and axillary hair.
- ***Rise in GnRH and gonadotropin levels:*** At ~7–8 years, hypothalamic sensitivity to gonadal steroids declines, leading to increased secretion of GnRH and consequently, pituitary gonadotropins. Initially, GnRH, LH and FSH are released in pulse-form during nights, but gradually raised levels are maintained throughout the day.

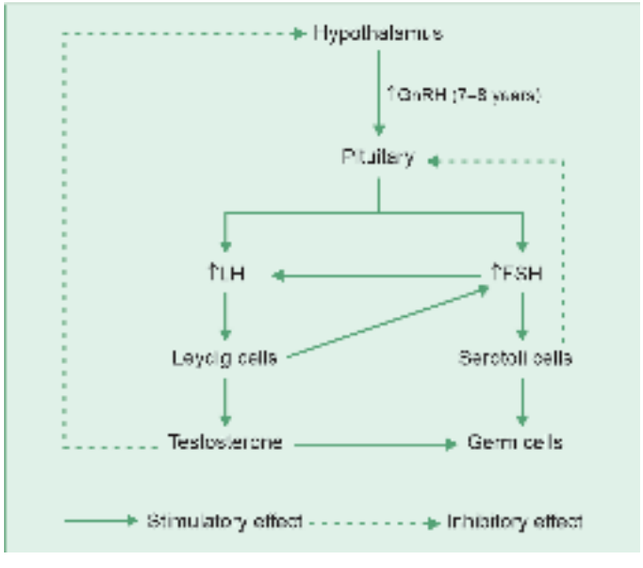

Fig. 22.6: Hormonal relationships at puberty.
adrenal androgens(DHEA/DHEAS) at 6–8 years lead to development of secondary sexual hair.

- ***Increased gonadal steroid secretion:*** Rising pituitary gonadotropin levels lead to gonadal maturation and increased secretion of gonadal steroids. In males, LH stimulates Leydig cells for testosterone production while FSH promotes development of seminiferous tubules and spermatogenesis. In females, LH promotes luteinization in ovaries and estrogen/progesterone secretion, while FSH is responsible for follicular development.
- ***Effects of gonadal steroids:*** Increased gonadal and adrenal steroid levels also leads to: (a) development of secondary sexual characteristics, (b) cyclic nature of menstruation, and (c) linear growth spurt as well as skeletal maturation.

Estrogen is prime determinant of breast growth, external genital changes and ovulation/menstruation in females; androgens, e.g. testosterone and its derivatives, are predominant hormones in males, leading to testicular and penile growth, typical body odor and voice changes. Adrenarche, i.e. development of sexual hair is mediated by androgens in both sexes.

Precocious puberty is defined as appearance of any of the secondary sexual characteristics before 8 years in girls and 9 years in boys; or onset of menarche before 10 years.

Etiology: Precocious puberty may be central or peripheral in origin, due to any cause of endogenous, exogenous or ectopic excess of puberty-determinant hormones **(Table 22.14)**.

- ***Central precocious puberty*** (CPP) is true precocious puberty due to premature activation of HPG axis (gonadotropin dependent). It is essentially isosexual, associated with true development of gonadal, reproductive and physical functions along with secondary sexual characteristics.
- **Peripheral precocious puberty** (PPP) is caused by exogenous administration or endogenous excessive production of sex steroids from any source (gonadal, adrenal, ectopic) not dependent on HPG axis (gonadotropin independent). Depending on sex-steroid preponderance, it may be isosexual or heterosexual and usually not associated with gonadal or reproductive maturation.

Incomplete variants of PPP include—(a) premature thelarche in females, due to excess of ovarian estrogen, (b) premature adrenarche/pubarche, due to excess of adrenal androgens, and (c) premature menarche, due to transient rise in ovarian activity.

Diagnostic evaluation of these children includes:

- *History with special reference to:* (a) age of onset, (b) similar family history regarding pubertal events, and (c) preceding intracranial disease or hormone therapy.
- *Physical examination* with special reference to: (a) anthropometry for linear growth, which will reveal tall stature (except in cases with associated hypothyroidism), (b) Marshal and Tanner staging for pubertal changes **(Table 13.2)**, (c) testicular size for tumors, (d) other endocrinal disturbances, e.g. hypothyroidism, CAH, etc. (e) intracranial disease, and (f) abdominal/pelvic lump (adrenal, gonadal tumors).
- *Baseline investigations* in all cases must include: (a) skeletal survey for bone age, and (b) serum gonadal steroid (estradiol and testosterone) levels. Bone age is advanced in complete precocious puberty, normal in incomplete variants of PPP and reduced in cases associated with hypothyroidism.
- *Detailed investigations* in cases with multiple signs of precocious puberty, advanced bone age and abnormal basal hormonal levels, including:
  - Hormonal assays for adrenal steroids (DHEAS, 17-OHP, androstenedione), HPG axis (GnRH stimulation test), LH/FSH levels, HCG levels (ectopic source) and thyroid function tests. LH/FSH levels are elevated in CPP and suppressed in PPP. GnRH stimulation test shows positive (pubertal) response CPP but not in PPP.
  - Radiological investigation with USG for uterus pelvis and adrenal masses, along with neuroimaging in suspected cases of CPP.

TABLE 22.14: Causes of precocious puberty

Gonadotropin dependent or central PP:
- Idiopathic (sporadic or familial)
- Intracranial (hypothalamic/pituitary) causes
- Congenital/developmental malformations
- *Post-infective:* Meningitis, encephalitis
- *Post-injury:* Trauma, surgery, radiation
- *Neoplastic:* Craniopharyngioma, hypothalamic hamartoma
- *Others:* Empty Sella syndrome, hypothyroidism

Gonadotropin independent or peripheral PP:

Isosexual peripheral precocious puberty (in girls)
- *Ovarian:* Benign cyst, gonadoblastoma*
- *Adrenal:* Adenoma, carcinoma
- Exogenous estrogen therapy
- Hypothyroidism, McCune-Albright syndrome

Isosexual peripheral precocious puberty (in boys)
- *Testicular:* Leydig cell tumor
- *Adrenal:* Congenital adrenal hyperplasia**
- *HCG secreting tumors:* Choriocarcinoma
- Exogenous androgen therapy
- Hypothyroidism, McCune-Albright syndrome

Heterosexual precocious puberty (in girls)
- Congenital adrenal hyperplasia
- Virilizing ovarian or adrenal neoplasms
- Exogenous androgen therapy

Heterosexual precocious puberty (in boys)
- Estrogen producing adrenal tumors
- Exogenous estrogen therapy

*/**Commonest cause in females and males respectively, excluding exogenous hormonal therapy

Management aims to suppress pubertal changes and achieve target height potential and includes:

- *Treatment of primary cause* or withdrawal of exogenous hormonal medications,
- *Specific hormonal inhibitors* in idiopathic/untreatable cases, as follows:
  - ***CPP:*** GnRH analogues, e.g. triptorelin/leuprolide as monthly IM preparations till desired age for puberty. Discontinuation of these analogues leads to resumption of puberty.
  - ***PPP:*** Treatment of the associated hormone deficiencies, e.g. eltroxin for hypothyroidism, hydrocortisone and fludrocortisone for CAH, along with surgical excision of tumors, if required. Aromatase inhibitors like letrozole, estrogen inhibitors, e.g. testolactone and anti-androgens like ketoconazole, spironolactone or cyproterone acetate may be used in selected cases.
- *Periodic monitoring* and psychological support.

Delayed puberty denotes maturational lag in HPG axis, clinically indicated by:

- Absence of the onset of breast development by 13 years in girls and testicular enlargement (> 3 ml) in boys by 14 years of age.
- A gap of >5 years between first sign of puberty and completion of genital growth/menarche, or
- Absence of menarche by 15 years in females.

Etiology: Delayed puberty is often constitutional, with similar family history and simultaneous lag in height and bone age. Pathological delay may be classified according to gonadotropin levels as hypogonadotropic hypogonadism due to central hypophyseal or pituitary causes and hypergondotropic hypogonadism due to peripheral causes **(Table 22.15)**.

Clinical evaluation is on same lines as for precocious puberty. History of orchitis should be additional enquired in males. Gonads should be carefully examined for stretched penile length and testicular volume. As many cases are chromosomal in origin, dysmorphic features may provide important clues for diagnosis. Afemale child with delayed puberty and short stature should be assessed for Turner syndrome.

Laboratory investigations should be more conservative as most cases are merely constitutional, though baseline investigations for bone age determination and exclusion of chronic illness, e.g. tuberculosis, renal function tests, are essential to exclude common causes.

Detailed investigations include:

- USG abdomen (gonadal/internal genitals) and CT/MRI brain (intracranial lesion).
- Karyotyping and cytogenetic studies for chromosomal defects.
- Relevant hormonal assays, as per clinical suspicion, e.g. thyroid function tests, sex-steroid levels (testosterone, estradiol, prolactin), basal and GnRH stimulated gonadotropin levels and HCG stimulation test in cases with non-palpable testis. A rise in testosterone levels after HCG indicates functioning testis.
- Gonadal biopsy in cases of suspected dysgenesis or DSD.

Management is conservative in most cases, including better nutrition, treatment of primary cause, e.g. infections, undernutrition, systemic illnesses and identifiable endocrinal causes, along with periodic follow-up.

Hormonal therapy should be deferred except in severe pubertal delay, as it may accelerate skeletal maturation and reduce ultimate adult height. Low-dose testosterone may be used in boys with severe delay to accelerate development of secondary sexual features and restore self-esteem; while low-dose daily estrogen therapy is used in girls till menstruation followed by cyclic therapy.

TABLE 22.15: Causes of delayed puberty

- **Constitutional**
- **Hypogonadotropic hypogonadism**
- Primary hypopituitarism
  - CNS infections, trauma, radiation, tumors
  - *Genetic:* Isolated GH or gonadotropin deficiency
- Secondary hypothalamic/pituitary suppression
  - Hyperprolactinemia
- Hypothyroidism
- Chronic infections, malnutrition, systemic disease
- *Others:* Laurence-Moon-Biedl syndrome

Hypergonadotropic hypogonadism

- Congenital gonadal dysgenesis
- *Chromosomal:* Klinefelter/Turner syndrome
- Disorders of steroid biosynthesis
- Acquired gonadal injury
  - *Infection:* Orchitis (mumps)
  - *Iatrogenic:* Surgery, radiation, chemotherapy
  - Trauma/torsion of testis

22.7 DIABETES MELLITUS

Diabetes mellitus (DM) is the commonest endocrine metabolic disorder of childhood, characterized by hyperglycemia due to deficiency of insulin or its action, with abnormal carbohydrate metabolism, and to some extent, the fat and protein metabolism.

According to the etiopathogensis, DM is classified as:

- *Type I or insulin dependent (T1DM),* due to severe insulin deficiency, which is common in children.
- *Type II or non-insulin dependent (T2DM)* due to insulin resistance, with/out insulinopenia, which is common in adults,
- *Secondary diabetes* due to drugs, e.g. steroids, genetic disorders of beta cell function (maturity onset diabetes of young or MODY), pancreatic disorders, intrauterine infections and other endocrinopathies, e.g. Cushing disease.

In addition, many children or adults have impaired glucose tolerance without definite evidence of DM, specially during stress, e.g. pregnancy, infections or after high-carbohydrate meals, which can be considered as a risk-factor for future DM.

22.7.1 TYPE I DIABETES MELLITUS (T1DM)

T1DM (Insulin-dependent diabetes mellitus) is the commonest cause of DM in childhood, with well defined diagnosis criteria **(Table 22.16)**. Glucose tolerance test is rarely required in children except in those with obesity or suspected T2DM, to detect impaired glucose tolerance.

Epidemiologically, exact prevalence of T1DM in Indian children is not well established, probably ranging from 0.1/1000/year, lesser than in Scandinavian countries (0.35/1000/year). Most cases are identified at two peaks-first between 5 and 7 years and second during adolescence.

Geographical and ethnic variations in prevalence of T1DM are probably related to variable frequency of susceptibility-genes on DQ beta chain of HLA system.

Etiopathogenesis: Progressively diminishing insulin secretion due to β-cell destruction of pancreas is the etiological hallmark of. T1DM is a multi-factorial disease, with three important contributing factors:

a. ***Autoimmunity:*** Considerable evidence indicates autoimmune basis for β-cell destruction, as suggested by: (a) presence of islet cell antibodies in 80–90% cases preceding the onset of clinical disease, (b) Lymphocytic infiltration around β-cells on autopsy, and (c) association with other autoimmune disorders, e.g. Addison's disease, Hashimoto thyroiditis, pernicious anemia, etc. Several genetic defects involving HLA antigens on chromosome 6 have been identified to increase the risk of autoimmune T1DM.

b. ***Inherent genetic susceptibility:*** T1DM is ~100 times more common in cases with homozygous absence of aspartic acid at position 57 of HLA-DQ β gene. However, it is also more common in certain genotypes of HLA-DR3 and DR4. Recurrence risk is about 2–7% in siblings or offsprings, while concordance rate in identical twins is 30–50%.

c. ***Trigger agents:*** Viral infections (mumps, rubella and Coxsackie's virus), stress and exposure to chemical toxins are known to trigger β-cell destruction via direct damage, unmasking islet cell antigens or shared antigens between organism and β-cells. Early introduction of cow milk has been suggested to increase the risk of T1DM in later life.

According to etiology, T1DM is also classified as *T1A* (Autoimmune) and *T1B* (Idiopathic), respectively.

TABLE 22.16: Diagnostic criteria for DM

Diabetes mellitus *(any one)*
- Suggestive symptoms with random BG >200 mg/dl
- Fasting BG level >126 mg/dl
- 2-hour post-prandial BG level >200 mg/dl
- Hemoglobin A1c ≥6.5% on repeated testing

Impaired glucose tolerance
- Fasting BG level <100–125 mg/dl,
- 2-hour post-prandial BG level >140–200 mg/dl

BG: Blood glucose

Pathophysiology: Insulin, secreted from β-cells of pancreas, is the prime regulator of blood glucose levels by its action on liver, muscle and adipose tissue. Quantum of insulin secretion is modulated by many neural, hormonal and substrate-related factors-increased in post-prandial states to augment glucose storage (glycogenesis) as well as diversion for protein and lipid synthesis; and decreased in fasting state to facilitate glycogenolysis and neoglucogenesis by counter-regulating hormones.

Progressive destruction of β-cells in T1DM lead to insulin deficiency and consequent metabolic disturbances, which may be sequentially described as:

- *Post-prandial hyperglycemia,* the earliest biochemical abnormality, due to relative lack of insulin reserve to control post-meal hyperglycemia.
- *Fasting/persistent hyperglycemia* in more severe cases, due to excessive glucose production in low insulin state.
- *Glycosuria,* once renal threshold for hyperglycemia (~180 mg/dl) is crossed, leading to osmotic dieresis and consequent features, e.g. polyuria, dehydration, dyselectrolytemia and polydipsia. Glucosuria usually appears when insulin levels drops below 20% of normal.
- *Increased secretion of counter-regulating hormones:* As insulin also increases cellular uptake of glucose, insulinopenia creates a state of cellular hypoglycemia, leading to increased secretion of counter-regulating hormones, e.g. ACTH, GH, epinephrine and glucagon, which accentuate hyperglycemia.

Diabetic ketoacidosis (DKA) is a state of—(a) hyper-osmolarity due to hyperglycemia, (b) ketosis due to increased lipolysis and neoglucogenesis leading to accumulation of free fatty acids, which are then diverted to form ketone bodies, i.e. β-hydroxybutyrate and acetoacetate, and (c) acidosis due to accumulation of ketoacids and urinary loss of cations, which are excreted in urine along with ketones.

Diabetic coma is the clinical effect of progressive hyper-osmolar dehydration, acidosis, electrolyte disturbances and poor glucose uptake by cerebral cells in a state of insulinopenia. A synopsis of mechanisms in diabetic pathophysiology and ketoacidosis/coma is shown in **Fig. 22.7**.

Clinical manifestations of DM depend on the severity of insulinopenia and rapidity of metabolic derangement. Important initial manifestations are:

- ***Classical tetrad*** of polyuria, polydipsia, polyphagia and unexplained weight loss in ~75% cases, though

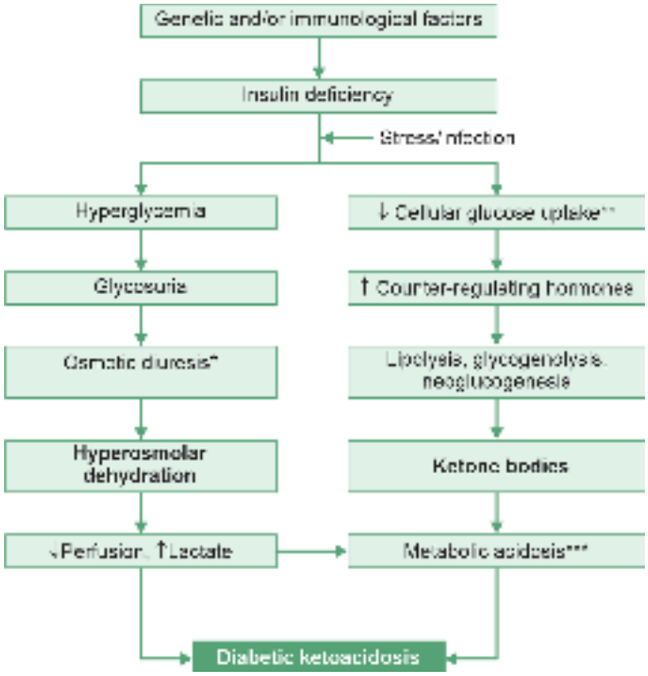

Fig. 22.7: Pathophysiology of diabetic ketoacidosis
*polyuria and polydipsia. **coma, due to cerebral glucopenia
***with hypokalemia, hypophosphatemia due to urinary loss

with shorter history than in adults (< 1 month). Unlike adults, recurrent/persistent pyogenic infections and candidiasis are rare presenting features in T1DM.

- ***Diabetic ketoacidosis*** is a presenting emergency 15–70% of newly diagnosed cases, often triggered by a viral infection or other stress factors. Known diabetics, who have defaulted on insulin or developed uncontrolled intercurrent infection, may also present with DKA.

  Clinical manifestations begin with recurrent vomiting, polyuria and abdominal pain, rapidly progressing to dehydration, metabolic acidosis (kussmaul breathing), fruity (acetonic) breathy odor, altered sensorium and coma. Important biochemical abnormalities include glucosuria, ketonuria, hyperglycemia, ketonemia and metabolic acidosis.
- ***Non-ketotic hyperosmolar coma*** is uncommon in children, presenting as severe hyperglycemia (>600 mg/dl) and other features of DKA, except ketosis. Absence of ketosis is attributed to severe hyperglycemia that blunts lipolytic effect of epinephrine. Focal CNS signs, e.g. seizures and hemiparesis are common, due to dehydration and hemoconcentration, leading to thromboembolic complications.

Diagnosis of T1DM depends on diagnostic criteria **(Table 22.16)**, though other investigations are required to assess the severity of metabolic derangements and include:

- Urine examination for glucose and ketones.
- *Blood glucose levels:* Random estimation is enough in symptomatic cases, while fasting and postprandial levels are needed in asymptomatic/ borderline cases.
- Serum electrolytes and acid–base analysis. Hyponatremia, hypokalemia and hypophosphatemia is common in DKA, apart from metabolic acidosis.
- Investigations for precipitating/co-existing infections.
- Special investigations for confirmation of T1DM etiology, e.g. C-peptide, anti-GAD 65 antibodies etc., are rarely required in practice.

Possibility of DKA should always be considered in a child with acute onset of unexplained vomiting and progressive coma and ***diagnostic criteria for DKA*** include:

- Hyperglycemia with BG levels >200 mg/dL
- Metabolic acidosis (pH < 7.3) with serum bicarbonate <18 mEq/L
- Ketonemia (β-hydroxybutyrate > 3 mmol/L) or moderate/severe ketonuria (≥ 2+)

D/D of DM includes other cause of hyperglycemia, e.g. drugs/poisonings, acute coma and renal glucosuria, e.g. Fanconi syndrome. T1DM should also be differentiated with T2DM or MODY, discussed later.

Management of T1DM presenting with DKA may be divided into 3 phases:

a. Emergency phase for management of DKA.
b. Transitional phase to normalise metabolic control.
c. Maintenance phase for long-term control of hypoglycemia.

Management of cases presenting without DKA begins with transitional phase only.

A. Emergency management of DKA aims to correct dehydration, dyselectrolytemia and acidosis as well as to initiate insulin therapy, with following steps:

1. ***Quick biochemical evaluation*** for initial severity of hyperglycemia, acidosis and electrolyte disturbances. Severity of DKA is classified as follows, to decide the need for further fluid therapy—(a) mild: pH < 7.3 and/or serum bicarbonate <18 mEq/L, (b) moderate: pH < 7.2 and/or serum bicarbonate < 15 mEq/L, and (c) severe: pH < 7.1 and/or serum bicarbonate <10 mEq/L.
2. ***IV fluid and electrolyte therapy,*** tailored with following principles:
   – *Amount of fluid* is calculated as maintenance plus deficit. Maintenance requirement is calculated as per body weight by Holiday-Segar formula (100 ml/kg for first 10 kg, 50 ml/kg for next 10 kg and 20 ml/kg for remaining kg), while deficit requirement is calculated based on severity of DKA, i.e. 5% (50 ml/kg), 7% (70 ml/kg) and 10% (100 ml/kg) for mild, moderate and severe DKA respectively. Deficit is corrected slowly over 24 to 48 hours.

- *Rate of infusion:* IV fluid therapy should begin with an initial bolus of 10–20 ml/kg over 30–60 min, followed by remaining calculated fluids over next 23 hours. In patients with shock, 20 ml/kg boluses may be given rapidly.
- *Type of fluid:* Rapid correction of hyperglycemia and hyperosmolarity may precipitate cerebral edema due to movement of fluids into intracellular space. Hence, normal saline or Ringer lactate must be used for first-hour correction, followed by N/2 saline till resolution of DKA. Dextrose containing fluids must be used when BG levels drop <250 mg/kg, to prevent insulin-induced hypoglycemia.
- *Potassium supplementation:* Total body potassium is depleted in DKA due to its extracellular movement and urinary loss in acidosis. Correction of hydration and acidosis along with insulin therapy leads to return of K^+ back into the cells, with hypokalemia. Potassium should be added in IV fluids (40 mEq/L) after first hour, after documenting urine output or normal/low serum potassium. Potassium phosphate and acetate preparations, though not easily available, are preferred over potassium chloride preparations, as chloride excess may aggravate acidosis.
- *Bicarbonate therapy:* Acidosis is usually corrected with fluid and insulin replacement. Bicarbonate therapy is generally contraindicated even in severe DKA, as it can worsen outcomes by causing paradoxical CNS acidosis. Bicarbonate use may be considered only in case of life-threatening hyperkalemia or unusually severe acidosis causing impaired cardiac contractility.
- *Phosphate supplementation:* Phosphate levels reduce in DKA due to osmotic diuresis, dilution following fluid resuscitation and insulin-mediated shift into intracellular compartment. Hypophosphatemia may rarely cause seizures, arrhythmias and rhabdomyolysis. Hence, use of potassium phosphate may be beneficial, wherever available, particularly in case of severe acidosis, with serum phosphate levels < 1 mg/dl.
- *Sodium supplementation:* while hyponatremia is common in DKA, no specific treatment is required except the use of normal saline for initial fluid therapy.
- *Monitoring* of these cases involve serial blood glucose and electrolyte levels, review of fluid intake/output chart and clinical monitoring, specially for signs of cerebral edema.

3. ***Insulin therapy*** should begin only after an hour of fluid therapy, which itself with reduce BG levels rapidly. Early insulin therapy may lead to drastic fall in plasma osmolality, hypokalemia and increased risk of cerebral edema.

Only regular insulin is used in DKA beginning with continuous IV infusion @ 0.05–0.1 U/kg/hr to accelerate movement of glucose into the cells. A separate IV cannula should be used for the insulin drip, and the tubing should be flushed before starting the infusion to saturate all sites. To prevent rapid fall in BG, DW 5% should be added in IV fluids once the BG levels falls to 250–300 mg/dL.

If hypoglycemia still occurs, the dextrose concentration may be increased to 10% or 12.5% rather than stopping insulin, as the main function of insulin administration in DKA is to suppress ketoacidosis. Glucose concentration must be adjusted to ensure that BG levels do not fall faster than 90–100 mg/hr.

Oral feeds must be started as early as possible, to prepare the patient for transitional phase.

B. Transitional phase begins after: (a) correction of acidosis and hypokalemia, (b) return of blood glucose levels <300 ml/kg, and (c) establishment of adequate oral intake.

Management of children presenting without DKA also begins with this phase, which aims to:

- Identify and treat the precipitating cause of DKA.
- Adjust the dose of regular insulin as per oral intake.
- Educate patient/parents about self-monitoring, self-insulin injection and symptoms of hypoglycemia (insulin shock).

Insulin therapy in this phase involves replacement of IV insulin with SC injections of regular insulin 0.1–0.25 U/kg 6–8 hourly immediately before meals along with simultaneous pre-meal and 2-hour post-meal BG monitoring for next 2–3 days. 24-hour regular insulin requirement at the end of this adjustment forms the basis for doses of subsequent long-term insulin therapy.

C. Long-term management aims to provide near normal control of hyperglycemia, while avoiding hypoglycemia. Life-long subcutaneous insulin therapy is essential in all cases of T1DM, along with dietary control. Oral hypoglycemic agents are not effective in these cases. Attempts to replace parenteral insulin with oral insulin therapy or pancreatic transplant, etc. are still in experimental stage. Important principles of long-term management include:

- **Insulin therapy:** Old generation pork/beef insulins have been now replaced by recombinant human insulins with different onset and duration of action **(Table 22.17)**, In DKA as well as in conditions of

TABLE 22.17: Classification of insulin preparations according to the onset and duration of action

Preparation	*Onset*	*Duration*
Rapid acting (Lispro, Aspart)	5–10 min	3–5 hr
Short acting (Regular)	30–60 min	5–8 hr
Intermediate acting (Lente, NPH)	2–4 hr	12–24 hr
Long-acting (Glargine, Detemir)	1–4 hr	20–24 hr
Ultra long-acting (Degludec)	30–90 min	>42 hr

stress, e.g. infection, surgery, etc. only rapid-acting or short-acting insulins must be used to permit quick adjustment of doses.

- *Basal-bolus regimen* is the preferred choice for insulin therapy in children without DKA, involving a single daily dose of long-acting Insulin (basal) along with multiple (3–4) doses of short/rapid acting insulin every day (bolus). Fixed dose combinations of short + intermediate acting insulins must be avoided in children.

  Continuous subcutaneous infusion by an external insulin pump, is the preferred alternative to basal-bolus regimen, which uses only rapid-acting insulin delivered at a predetermined rate with additional boluses at meal time. *Closed-loop hybrid systems* to monitor BG levels using subcutaneous sensors and adjust the insulin dose automatically are also approved for use in children.
- To being with, pre-pubertal children generally require 0.7–1.0 IU/kg/day of Insulin, while higher doses are needed (1–2 IU/kg/day) in adolescents. In basal-bolus regimen, 30–50% of total calculated daily dose must be given as a basal long-acting analog (Glargine, Detemir, Degludec) for smoother 24-hour control, while the remaining dose must distributed among pre-meal boluses of short-acting insulin (Lispro, Aspart) to prevent post-meal surge in BG levels.
- Subcutaneously insulin must be injected via special syringes or pre-filled pens over abdomen, thigh, buttocks or upper arm. Sites should be rotated periodically to avoid local lipodystrophy.
- BG monitoring before each meal is advised to decide the insulin dose based on dietary carbohydrate counting to achieve good glycemic control.
- Further modifications in basal dose depend on state of glycemic control, which should be monitored at least twice a day (pre-breakfast and pre-dinner) by glucostix in blood **(Table 22.18)**.

TABLE 22.18: Insulin dose modifications

Pre-lunch hypoglycemia	↓ pre-breakfast bolus insulin by 10%
Pre-lunch hyperglycemia	↑ pre-breakfast bolus insulin by 10%
Pre-dinner hypoglycemia	↓ pre-lunch bolus insulin by 10%, give evening snack* before play
Pre-dinner hyperglycemia	↑ pre-lunch bolus insulin by 10%
Pre-breakfast hypoglycemia	↓ Basal insulin, if given at night
Pre-breakfast hyperglycemia	Check BG at 4 am, • If low, ↓ night basal insulin • If high, ↑ night basal insulin
During infection / fever	Monitor BG frequently Switch to adjusted doses of rapid insulin

Basal insulin: Long acting, bolus Insulin: short acting
*If vigorous physical activity expected in evening

- **Diet:** Strict dietary regulations are neither practical nor desirable in T1DM children, though it is preferable to follow certain dietary principles:
  - Total caloric intake should be same as for a normal child, given as a mixture of carbohydrates (55%), fats (30%) and proteins (15%). High-fiber diet facilitates better control.
  - At least 70% of carbohydrates must be given as complex starch. Refined sugar/carbonated beverages should be avoided and safety of artificial sweeteners, e.g. saccharin and aspartame, is not established in children.
- **Exercise:** No exercise restriction is necessary, though some cases may develop hypoglycemia during/after exercise due to increased glucose demands and/or increased insulin absorption from the injection site. It is advisable to consume additional carbohydrate-rich food items before strenuous exercise, and keep a glucose/candy or sugar-cube handy in event of hypoglycemia. In planned exercise, previous insulin dose may be reduced by 10%.
- **Monitoring** is an essential part of management in DM and may be divided into three components—(a) self-monitoring, (b) periodic BG monitoring, and (c) monitoring of long-term glycemic control.
  - ***Self-monitoring*** is the basic tool to assess diabetic control, which requires proper parental counseling and training for regular pre-meal (and ideally post-meal too) capillary BG monitoring with glucometer. A target fasting BG of 90–130 mg/dl, post-prandial BG of 140–160 mg/dl or average bed-time BG of 110–150 mg/dl is considered as optimum.

    To reduce the number of pricks, continuous glucose monitoring systems (CGMS) are also available, which once fixed, function for 14 days and come with a reader which flashes the glucose reading.
  - Periodic BG testing in hospital is desirable only if self-monitoring is not reliable or in poorly controlled cases. Random blood glucose levels are of no use in assessment of control.
  - **Long-term glycemic control** is best monitored with glycosylated Hb **(HbA1c)** levels-a fraction of Hb, which is non-enzymatically attached to glucose in peripheral blood. Formation of HbA1c is an irreversible reaction and as the life span of RBCs is ~120 days, HbA1c levels reflect status of glycemic control in preceding 3 months. HbA1c levels of <7% are recommended as the indicator of optimum long-term glycemic control in children. HbA1c measurements are advisable every 3–4 months.

- **Psychological support** to child and family is as important as the medical treatment to ensure proper compliance and quality of life in DM.

Special issues in management of IDDM:

Honeymoon period: After initial stabilization of DKA, ~75% children show progressive reduction in their insulin requirements during next few weeks/months (honeymoon period) before rising again. This phenomena indicates some residual β-cell function and insulin secretion during this period, as measured by C-peptide levels. Exact cause of DKA in these cases despite residual β-cell function is unclear, probably relates to sudden rise in counter-regulatory hormone levels during stress events, e.g. infections, which couldn't be compensated by borderline insulin levels.

Somogyi phenomenon denotes early-morning hypoglycemic episodes on insulin therapy, followed by hyperglycemia/glucosuria with/without ketonuria after 4–5 hours. It is believed to be due to outpouring of counter-regulatory hormones in response to early morning insulin-induced hypoglycemia. Treatment involves reduction of night time Glargine (basal insulin) dose by 10–15% to prevent early morning hypoglycaemia.

Dawn phenomenon denotes early-morning hyperglycemia, not preceded by hypoglycemia (d/d Somogyi phenomenon). It is probably due to waning effect of evening insulin or normal nocturnal surge in GH/steroid secretion and must be treated by increasing night time Glargine by 10–15%.

As the treatment of somogyi and Dawn phenomena is exactly opposite, it is important of differentiate between the two, by measuring BG levels at 3, 4 and 7 AM. Absence of hypoglycemia in first two samples rules out Somogyi phenomenon.

Brittle diabetes denotes wide fluctuations in BG levels despite frequent adjustments in insulin doses. These cases may be treated by increasing frequency of insulin administration or by changing the type of insulin.

Hypoglycemic episodes (Insulin shock) are common in diabetics, due to honeymoon phase, Somogyi phenomenon, insulin overdose, fasting and strenuous exercise. These cases present with signs of sympathetic overactivity followed by neuroglycopenic symptoms, e.g. excessive sweating, palpitation, trembling and altered sensorium due to outpouring of counter-regulating hormones. Unlike DKA, hypoglycemic coma develops within few minutes and parents should be trained to recognize and treat it with immediate glucose consumption.

Infections in diabetics: Intercurrent infections or illnesses may destabilize glycemic state in T1DM, with higher risk of developing hyperglycemia and ketoacidosis despite vomiting and poor oral intake. General guidelines to manage a sick day in diabetic children are as follows:

- Do not omit the insulin dose but reduce it as per BG levels, if necessary.
- Monitor BG levels and urine ketones more frequently, at least every 4 hours.
- If BG levels exceed 300 mg/dl anytime, give additional dose of regular/rapid insulin equal to 10% of total insulin dose.
- If BG drops <100 mg/dl anytime, give sugar water and omit longer-acting insulin, replacing it with frequent doses of regular/rapid acting Insulin as per BG monitoring.
- Hospitalize if develops vomiting, oliguria, breathlessness or drowsiness.

Surgery in diabetics: During major surgeries, it is advised to provide continuous IV insulin infusion along with potassium-containing normal saline or N/2 saline with Dextrose 5% during intraoperative and immediate post-operative period. Patient may be switched back to original schedule after oral intake is established. However in minor surgeries, it is enough to give regular morning dose on the day of surgery and an additional dose of SC 0.25 U/kg regular insulin after surgery.

Late complications: Short stature and delayed puberty are commonest problems in IDDM, recognized during childhood. With improving survival, other late complications are also being increasing recognized after >15–20 years of diagnosis, e.g. retinopathy and lenticular opacities, nephropathy and neuropathy. Development of complications is directly related to status of long-term glycemic control. Rare complications include osteopenia, limited joint mobility syndrome and Mauriac syndrome (severe short stature with delayed puberty, waxy skin and hepatomegaly)

All cases of TDM should be monitored for hypertension during each visit and annually for nephropathy, retinopathy, neuropathy and dyslipidemia from 10 years of age onwards. They must also be assessed for thyroid disease (every 1–2 years) and celiac disease (at 2 and 5 years age).

Other uncommon but important forms of DM in children are as follows:

Type II diabetes (T2DM) or non-insulin dependent diabetes mellitus is the commonest type of DM in adults, due to relative insulin resistance with or without variable degree of insulin deficiency. Once considered as rarity in childhood, incidence of T2DM has shown dramatic rise in adolescents during recent years, probably due to rising incidence of obesity that blunts the insulin response. While detailed discussion of T2DM is beyond the scope of this book, important differences between T1DM and T2DM are given in **Table 22.19**.

Maturity onset diabetes mellitus is a heterogeneous group of autosomal dominant defects in β-cell functions with impaired insulin secretion in response to hyperglycemia (not the insulin resistance).

TABLE 22.19: Type I *vs.* Type II diabetes mellitus

Features	*Type I*	*Type II*
Primary defect	Insulinopenia	Insulin resistance
Age of onset	<15 years	>30 years
Family history	Uncommon	Common
Obesity	Absent	Common
Clinical Onset	Often acute	Often gradual
D. ketoacidosis	Common	Rare
Primary therapy	Insulin	Diet, oral drugs

Diagnostic criteria for MODY essentially include:

- History of DM in at least three generations, confirming vertical transmission of AD defect, and
- Onset or diagnosis of disease before 25 years of age.

Various mutations have been identified so far for MODY, the common ones being:

- *MODY-2*, involving glucokinase genes at chromosome 7p, which presents with mild chronic hypoglycemia or impaired glucose tolerance; and
- *MODY-1 or-3*, involving HNF-4 gene at chromosome 20q or HNF-1 gene at chromosome 12q respectively, both presenting with progressively severe diabetes and vascular complications.

Some other forms of Diabetes due to secondary causes e.g. cystic fibrosis-related diabetes (CFRD), fibrocalculous pancreatic diabetes (FCPD), drug-induced diabetes, and lipodystrophic diabetes are also recognized.

22.8 HYPOGLYCEMIA

Hypoglycemia beyond first 72 hours of life is defined as :

- Blood glucose levels < 45 mg/dl*
- Symptoms compatible with hypoglycemia, and
- Resolution of symptoms after glucose therapy.

*However, some children may be symptomatic even at blood glucose levels between 45–55 mg/dl.

Present chapter mainly deals with post-neonatal hypoglycemia, while neonatal hypoglycemia is discussed elsewhere (Ch 12.18).

Etiology: Maintenance of normoglycemia depends on: (a) adequate substrate (glucose) supply, (b) appropriate hormonal control, and (c) appropriate metabolic pathways. Insulin is the hypoglycemic hormone while counter-regulatory hormones, e.g. GH, cortisol, glucagon and epinephrine, increase BG levels via various metabolic pathways.

Hypoglycemia may develop due to:

- *Substrate deficiency*, e.g. prolonged fasting or inadequate energy stores, e.g. low birth weight or severe malnutrition.

TABLE 22.20: Causes of hypoglycemia beyond neonatal period

Persistent/recurrent hypoglycemia

- **Substrate deficiency**
  - Ketotic hypoglycemia
- **Hyperinsulinemic states**
  - Congenital hyperinsulinism
  - Familial or sporadic (Nesidioblastosis)
  - β-cell adenoma in older children
  - Beckwith-Wiedemann syndrome
- **Deficiency of counter-regulatory hormones**
  - Growth hormone deficiency
  - Cortisol deficiency/Addison disease
  - Glucagon deficiency
- **Metabolic defects**
  - Glycogen storage disorders
  - Fructose 1, 6 diphosphate deficiency
  - Galactosemia
  - Fatty acid oxidation defects
  - Branched chain ketonuria e.g. MSUD
- **Transient hypoglycemia**
  - Severe malnutrition
  - Poisoning e.g. salicylates, alcohol, quinine
  - Liver disease e.g. Reye syndrome
  - Septicemia
  - *Iatrogenic:* Insulin therapy
- **Pseudohypoglycemia in polycythemia**

MSUD: Maple syrup urine disease

- *Hormonal imbalance*, e.g. hyperinsulinemic states or deficiency of counter-regulatory hormones
- *Metabolic disorders* involving glycogenolysis or neoglucogenesis.

Hypoglycemia in newborns is usually transient and indicates substrate deficiency due to delayed feeding or poor energy stores, while post-neonatal hypoglycemia is usually endocrinal or metabolic in origin and tends to be recurrent or persistent **(Table 22.20)**.

Clinical manifestations of hypoglycemia result from both-direct depression of CNS due to glucopenia and compensatory hypersecretion of epinephrine-principle counter-regulatory hormone, as follows:

- *Signs of cerebral glucopenia:* headache, confusion, altered sensorium or coma, seizures and ataxia.
- *Signs of epinephrine excess:* tachycardia, excessive perspiration, pallor, weakness, anxiety, vomiting.

Clinical features of hypoglycemia in infancy are relatively non-specific and include jitteriness, feeding difficulties, hypotonia, hypothermia and pallor.

Diagnosis of hypoglycemia per se is based on BG levels during the attack, while etiological diagnosis in unexplained, persistent or recurrent hypoglycemia requires detailed investigations for endocrinal/metabolic causes. Important investigations in these cases include:

- Serum insulin levels to exclude hyperinsulinemic states
- Growth hormone and cortisol levels for counter-regulatory hormonal defects,

- Serum lactate, free fatty acids and Ketones (β-hydroxybutyrate) levels for metabolic defects, and
- Urine examination for ketones.

All samples must be collected before the treatment for valid results.

Treatment: Acute hypoglycemia is an emergency and irrespective of the cause, the treatment is same – IV Dextrose 10% 2 ml/kg as bolus, followed by continuous infusion at the rate of 6–12 mg/kg/min adjusted with frequent blood glucose monitoring.

Refractory hypoglycemia to above treatment may be treated with IV hydrocortisone (5 mg/kg/d q8hr) or PO Diazoxide or SC Octreotide. Further treatment depends on the identified cause.

Some important causes of persistent/recurrent hypoglycemia in children are as follows:

Ketotic hypoglycemia is the commonest cause of new-onset recurrent hypoglycemia beyond infancy, usually seen in 2–5 year age-group. Exact cause is unknown, probably relates to defective mobilization of alanine from muscles for neoglucogenesis.

Clinically, these cases are generally thin built with history of low birth weight and present with recurrent early morning symptomatic hypoglycemia after prolonged fasting or during intercurrent illnesses.

Diagnosis rests on exclusion of other causes for ketotic hypoglycemia. A shorter period of fasting for 12–18 hours may induce hypoglycemia with ketosis/ketonuria in these cases, as compared to >36 hours required in normal children.

Management includes treatment of acute episode with dextrose infusion as well as prevention of recurrence by avoidance of fasting, frequent high-protein, high-carbohydrate meals and treatment of intercurrent illnesses. Most cases resolve spontaneously by 8–9 years of age.

Bedtime administration of corn starch helps to prevent early morning hypoglycaemia, particularly during illnesses.

Hyperinsulinemic states denote failure of the suppression of insulin secretion despite hypoglycemia.

- *Transient hyperinsulinemia* is common in neonates of diabetic mother due to fetal islet cell hyperplasia in response to high maternal blood glucose, which recovers spontaneously.
- *Persistent hyperinsulinemia* may be due to: (a) familial/sporadic congenital hyperinsulinism (nesidioblastosis) since infancy, (b) islet cell adenoma in older children, and (c) Beckwith-Wiedemann syndrome.

Neonates and infants with CHI are more prone to brain injury as hyperinsulinism not only causes hypoglycemic damage but also suppresses production of ketones – the alternative fuel to the brain.

Clinically, hyperinsulinemic babies tend to have larger body size with voracious appetite and recurrent episodes of severe hypoglycemia within 1–3 hours of feeding.

Diagnosis may be confirmed by serum insulin levels (>5–10 µU/ml) during an episode of hypoglycemia, along with characteristic absence of ketosis or ketonuria (d/d counter-regulatory hormonal defects).

Treatment, after acute hypoglycemic control with dextrose infusions, includes PO Diazoxide (10–25 mg/kg/d q6hr) or SC Octreotide (5 µg/kg/dose q6hr) to suppress insulin secretion. However, most cases of nesidioblastosis or islet cell adenoma need surgery with subtotal pancreatectomy or tumor removal respectively.

Deficiency of counter-regulatory hormones, e.g. GH or cortisol deficiency, present with signs of primary disease as well as ketosis/ketonuria (d/d hyperinsulinemia) during hypoglycemic episodes and elevated free fatty acids.

Metabolic disorders with hypoglycemia include disorders of glycogenolysis (GSD type Ia) or neoglucogenesis (rare fructose 1–6 diphosphatase deficiency), fatty acid oxidation defects (medium chain fatty acid aceyl-CoA dehydrogenase deficiency) and others, e.g. galactosemia. Hypoglycemia in all of them is associated with ketosis/ketonuria, except fatty acid oxidation defects.

Reactive hypoglycemia denotes hypoglycemia after 2–3 hours of meals, specially seen in children who later develop IDDM or after gastric surgery (dumping syndrome) due to rapid gastric emptying leading to rapid rise in BG levels and consequent increase in insulin secretion.

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CHAPTER

23

Disorders of Bones and Joints

Mukesh Agrawal

Orthopedic problems in childhood deserve special attention for two reasons: (a) many of them are mere developmental aberrations which correct spontaneously over time and do not need any intervention, e.g. physiological bowing, and (b) even a minor defect of growing skeleton may lead to long-term adverse effects on childhood growth and development.

23.1 BASIC CONSIDERATIONS

Embryologically, all bones of body are mesodermal in origin, developing from the mesenchymal cells by two different mechanisms:

a. *Enchondral bone formation,* i.e. initial differentiation of mesenchymal cells into cartilage during intrauterine life, which is gradually replaced by bony tissue *in utero* or postnatally. Long bones and bones of skull base develop by this mechanism.
b. *Membranous bone formation,* i.e. direct differentiation of mesenchymal cells into bony tissue, without cartilage formation. Bones of skull vault develop by this mechanism.

Enchondral bone formation, the predominant mode of bone development, begins at the ends of long cartilaginous bones (physes or physeal plate) and extends distally towards the ends (epiphysis) or towards the shaft (metaphysis and diaphysis). Initially, these bones are non-calcified and vulnerable to extrinsic pressure, i.e. intrauterine pressure-a common cause of developmental deformities. Process of ossification begins with appearance of various ossification centers in late gestation or postnatal period, which continues till late childhood or adolescence.

Even after formation, bones are subject to constant turnover with *new bone formation by osteoblasts* at epiphyseal plate and subperiosteal region, as well as *bone resorption by osteoclasts* at subperiosteal region.

Structurally, each bone consists of four majorcomponents:

a. A mash-work of *collagen* fibers, derived from osteoblasts, i.e. modified mesenchymal cells.
b. *Ground matrix*, a cementing substance to bind collagen network, composed of various substances, e.g. mucopolysaccharides, mucoproteins and phospholipids.
c. *Bone cells* of three major types—osteocytes, osteoblasts and osteoclasts
d. *Inorganic minerals*, e.g. Ca^{++} and PO_4^{-} salts to provide essential strength for above architecture.

Pathologically, rapidly growing bones of a fetus or a child are exposed to various extrinsic and intrinsic adverse factors, leading to various orthopedic disorders, as follows:

- *Intrinsic defects* in formation of bony framework, e.g. congenital anomalies and skeletal dysplasias.
- *Extrinsic factors* to affect growth of normally formed bones, e.g. intrauterine pressure or posture, post-natal growth and trauma/disease.
- *Defective mineralization* or demineralization of bones, e.g. rickets or osteomalacia
- *Defective vascularization* or devascularization, e.g. osteochondroses
- *Defective resorption* or *turnover* of bones, e.g. post-infective/traumatic healing or tumors.

Etiologically, common orthopedic problems in children may be broadly divided in: (a) developmental bone disorders, (b) inherited skeletal dysplasias, (c) bones and joint infections, (d) skeletal trauma and fractures, (e) osteochondroses or avascular disorders, and (f) bone tumors and masses; which are discussed in this chapter. For disorders of mineralization, e.g. rickets *see* Chapter 6.5.

23.2 DEVELOPMENTAL BONE DISORDERS

Developmental bone disorders may be broadly divided into two groups—(a) *congenital malformations,* and (b) *developmental defects* of normally formed skeleton, which is deformed subsequently due to abnormal uterine posture or pressure.

While congenital malformations are obvious at birth and remain static throughout the life, developmental

defects are easily missed in younger children, only to manifest later, after worsening of deformity following rapid musculoskeletal growth.

23.2.1 CRANIOFACIAL MALFORMATIONS

Craniofacial skeletal abnormalities usually represent true bony malformations and not the developmental defects, as head is least affected by uterine pressure. Most of these defects are important indicators of genetic defects and intrauterine insults, frequently associated with neurological and ocular defects. Some important craniofacial skeletal malformations are as follows:

Craniosynostosis denotes *premature closure of the one or more cranial sutures*. Normally, the coronal, sagittal and lamboid sutures close during second decade of life, while the metopic suture closes much earlier by 2 years. Premature sutural closure arrests growth of calvarium in a direction at right angle of the fused suture, leading to abnormal shapes of skull and restricted brain growth.

Etiology: Craniosynostosis may be primary (present at birth) or secondary.

Primary craniosynostosis is usually associated with Genetic syndromes, e.g. *Crouzon syndrome* (acrocephaly with proptosis and mandibular hypoplasia), *Alport syndrome* (Acrocephaly with polysyndactyly), *Carpenter syndrome* (Clover-leaf skull deformity with mental retardation, polysyndactyly and congenital heart defects).

Secondary craniosynostosis is usually seen in microcephaly or metabolic disorders, e.g. hypophosphatasia and idiopathic hypocalcemia.

Clinically, these cases present with**:** (a) palpable sutures as prominent bony ridge, (b) abnormal skull shapes **(Fig. 23.1)**, and (c) neurological abnormalities, e.g. raised intracranial pressure, hydrocephalus, and (d) ocular abnormalities, e.g. proptosis, optic atrophy, etc. Deafness is common.

Common skull shape abnormalities in craniosynostosis include:

- *Scaphocephaly* (*sagittal suture fusion)*: Long, narrow skull with mid-line ridge.
- *Brachycephaly* (*bilateral coronal/lamboidal suture fusion*): Flat, broad face with widely set eyes.
- *Plagiocephaly* (*unilateral coronal suture fusion*): Asymmetric face, prominent on opposite side.
- *Acro-/Oxycephaly (multi-sutural fusion)*: Long, cone-shaped head, with shallow orbits.
- *Trigonocephaly* (*Metopic sutures fusion*): Wedge-shaped head with hypotelorism.

Diagnosis is mainly clinical, supported by skull X-rays to confirm sutural fusion and CT/MRI to identify the neurological abnormalities.

Management depends on the extent of sutural fusions. While single sutural fusions are usually asymptomatic, multiple/severe sutural involvement may be associated with neuro-ocular complications and needs early craniotomy to prevent further restriction of brain growth.

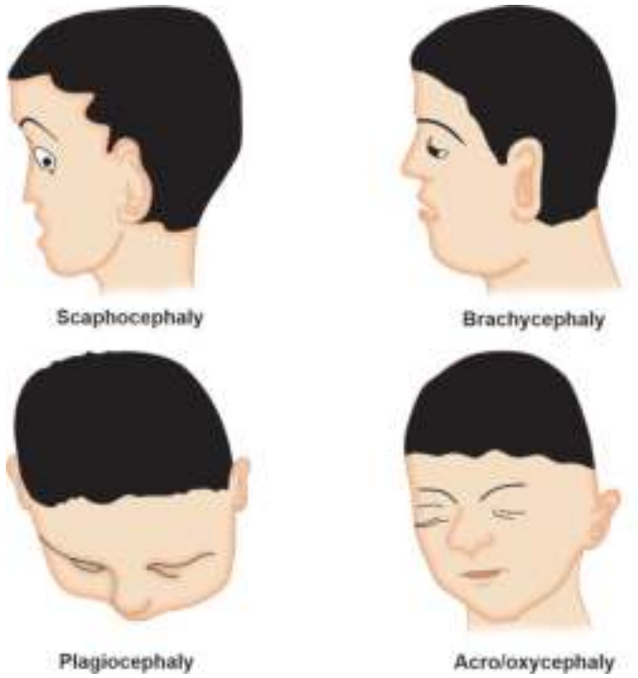

Fig. 23.1: **Craniosynostosis: Common skull shapes.**

Lacunar skull is characterized by bony defects in frontal/parietal regions of skull, which appear as irregular patches of rarefaction of X-rays. It is usually seen in craniosynostosis or associated with meningocele.

Microcephaly is an important cause of mental retardation, defined as *head circumference < 3rd centile for age.*

Etiologically, it may be classified as *primary* or inherited defect and *secondary*, due to *in utero* or early postnatal insult to growing brain (*see* **Table 18.25)**.

Clinically, microcephaly is associated with reduced velocity of postnatal head growth and developmental retardation, along with seizures and other features of chromosomal disorder or intrauterine infections. Abnormal facial appearance with slanting forehead and prominent nose and ears are more common in primary microcephaly (D/D secondary microcephaly)

Diagnosis of microcephaly *per se* rests on head circumference, though etiological diagnosis requires neuroimaging, karyotyping and serological studies for intrauterine infections. Salient differentiating features between microcephaly and craniosynostosis are given in **Table 23.1**.

Management of microcephaly is directed towards the primary cause, though developmental outcome is universally poor.

Facial dysmorphism is an important indicator of chromosomal disorders or underlying systemic disorders. Apart

TABLE 23.1: D/D microcephaly *vs* craniosynostosis

Feature	*Microcephaly*	*Craniosynostosis*
Head size	<3rd centile	Normal/↓
Sutures/AF	Normal/small	Prominent/fused
Head Shape	Small head	Variable shapes*
MR	++, since birth	±, may be late
Other lesions	Common[1]	Uncommon[2]

AF: Anterior fontanel, **MR:** Mental retardation, **see* Fig. 23.1

[1] signs of chromosomal defects or intrauterine infections

[2] except secondary neuro-ocular abnormalities

from abnormal facial appearance in microcephaly or craniosynostosis, discussed earlier, other important facial defects are as follows:

Hypertelorism, i.e. *wide separation of eyes due to relative overgrowth of lesser wings of sphenoid*, is confirmed by measuring interorbital distance. A *Canthal index* (inner canthal distance/outer canthal distance × 100) of >38–40 at any age suggests hypertelorism.

Hypertelorism is seen in many chromosomal disorders, e.g. Down syndrome, craniosynostosis, e.g. Alport/Crouzon syndrome, *and* CNS anomalies, e.g. frontal encephalocele. Pseudohypertelorism is common in children with broad nasal bridge or epicanthic folds.

Hypotelorism with Canthal index of <32, is relatively uncommon, usually associated with craniosynostosis, Patau syndrome (trisomy 13) and CNS defects, e.g. holoprosencephaly.

Depressed nasal bridge may be familial, chromosomal (mongolism), traumatic or post-infective, e.g. in syphilis.

Micrognathia/retrognathia (Mandibular hypoplasia) is an important craniofacial abnormality in many syndromes and indicates defective development of first visceral/aortic arch in fetus.

Pierre Robin syndrome is characterized by a triad of: (a) micrognathia with relative macroglossia, (b) cleft palate, and (c) glossoptosis, with/without other defects, e.g. CHDs or mental retardation. Most cases die in infancy due to choking or aspiration, though survivors show good jaw growth with normalization of facial profile by ~5 years. These babies should be nursed in prone position with gavage feeding during early life to prevent choking. Temporary fixation of the tongue to alveolar margins may be necessary in severe cases to prevent glossoptosis.

Treacher-Collins syndrome is characterized by: (a) typical *triangular face* due to severe mandibular hypoplasia, (b) ocular malformations, e.g. antimongoloid slant or lid coloboma, and (c) ear deformities, e.g. microtia, absence of ear canal, preauricular skin tags or *sinuses/dimples on a line from ear tragus to angle of mouth*. Deafness, CHDs and mental retardation are common.

Prognathia (mandibular hyperplasia) may be familial or seen in chromosomal disorders or endocrinal defects, e.g. acromegaly.

23.2.2 DEVELOPMENTAL LIMB DISORDERS

Maximum effect of *in utero* fetal position and pressure is obvious on limbs, leading to torsion and angular alignments of long bones as well as some extent of joint and muscle contractures. Even normal newborns have 20–30 flexion contractures at hip and knee, which disappears by 4–6 months of age. These deformities tend to be exaggerated in primi mothers and oligohydramnios.

Primary challenge in developmental limb disorders is to differentiate between physiological and pathological aberrations for rational management

Congenital limb malformations are relatively uncommon and include:

Limb deficiency *amelia* (complete absence of limbs), *Phocomelia* (absence of proximal and middle segments, with hands/feet directly attached to trunk), *Hemimelia* (absence of distal and middle segments, with preserved arms/thighs), *Acheiria* (absence of hands/feet) and *Adactylia* (absence of fingers or toes).

While fetal thalidomide exposure was once the commonest cause of limb-deficiency defects, currently most of these malformations are sporadic and isolated defects, probably representing intrauterine amputation of developing fetal limb by amniotic constriction bands.

Partial or minor limb defects are also seen in rare sporadic syndromes, e.g. *Holt-Oram syndrome* (with CHDs), *Cornelia de Lange syndrome*, etc. *Radial club hand* (complete or partial absence of radius) is a rare but important limb defect, seen in VATER association (Chapter 12.19) or Holt-Oram syndrome.

Amniotic constriction bands (*annular bands or constriction rings*) due to entrapment of affected part in amniotic membranes are common over toes and fingers, but may also involve whole or part of limb circumference. Severe constriction rings may cause auto-amputation of distal parts **(Fig. 25.2)**.

Digit abnormalities, e.g. *polydactyly* (super-numerary digits) or *syndactyly* (fusion of digits) are common and usually cosmetic birth defects. However, some of them are associated with other malformations, e.g. craniosynostosis, chromosomal trisomies, fetal-hydantoin syndrome, cornelia de lange syndrome or oro-facial digital syndrome. Surgical excision of well-formed extra digit is preferred after infancy, though rudimentary digit may be ligated at birth to allow auto-amputation **(Fig. 23.2)**.

Brachydactyly (short, stubby fingers/toes) or *Clino-dactyly* (incurving of usually little finger) are minor phalangeal abnormalities, common in chromosomal disorders, e.g. Down syndrome, Rubinstein-Taybi syndrome, Turner syndrome, etc.

Congenital hemihypertrophy, i.e. *unilateral overgrowth* of whole or part of the body, may be associated with mental retardation, Wilms' tumor or adrenal

Fig. 23.2: **Polysyndactyly.**

carcinoma. Underlying tissues are normal in congenital hemihypertrophy, unlike *acquired hemihypertrophy* in neurofibromatosis, hemangioma or lymphangioma.

Fixed flexion deformities, limited to hand/feet are not uncommon due to stenosed tendon sheath and usually present with *Trigger thumbs/fingers* at terminal interphalangeal joint of hands and *Hammer toe* at proximal interphalangeal joint of toes. Although passive stretching/strapping may be useful in young infants, surgical release is often necessary to achieve full function.

Arthrogryposis multiplex congenita is a symptom complex characterized by multiple joint contractures at birth, leading to severe limb deformities. Though seen in many syndromes, commonest prototype is *Amyoplasia*, accounting for ~40% cases and discussed here.

Etiology is exactly unknown, suspected to be due to a fetal *neurological defect* with decreased number of anterior horn cells or fetal *myopathy*, leading to decreased fetal movements and subsequent *in utero* contractures.

Clinically, joint contractures are present in all limbs, more prominent in lower limbs, though variants with are known. Although contractures are essentially non-progressive, many cases die in infancy due to respiratory muscle involvement.

Diagnosis is clinical, followed by radiological evaluation for major orthopedic defects, e.g. spinal deformities and hip dislocation.

Treatment aims to achieve maximum function and reduce cosmetic deformities, with physiotherapy, orthotic support and surgical correction of major defects.

Incidentally, a mythological character in Mahabharat 'Astavakra' was probably a case of Arthrogryposis multiplex congenita.

Developmental dysplasia of hip (DDH), also referred as *congenital dislocation of hip* (CDH), is characterized by partial/complete and temporary/permanent *dislocation of femoral head from its acetabular cavity*, affecting stability of hip joint.

Etiology: Stability of hip joint depends on depth and configuration/angulation of acetabulum and strength of surrounding ligaments/muscles.

DDH may result from: (a) underdeveloped shallow acetabulum or small/anteverted femoral head, (b) ligamental laxity, due to neuromuscular disorders or maternal estrogen effect, or (c) abnormal hip posture during/after delivery, which dislocates the hip and keeps it dislocated.

Early DDH is usually relocatable, but subsequent contractures in long-standing cases turn it into a permanent deformity.

Epidemiology: DDH is more common in females (9:1), first-born child (~60%), full term breech deliveries (30–50%) and in presence of similar family history (? hereditary). It is relatively less common in India than in western countries, probably due to the Indian practice of carrying the child on waist with abducted hips that prevents dislocation of hip despite anatomical abnormality.

Clinically, DDH may be bilateral or unilateral, usually on left side (60%) or hip is usually normal at birth and dislocates postnatally on flexion/adduction of hip, with following signs:

- Asymmetrical skin folds in groin/thigh;
- Restricted abduction at hip, leading to difficulty in changing of diapers; **(Fig. 23.3A)**
- *Galeazzi sign, i.e.* apparent shortening of limbs with uneven knee-level, when knees and hips are flexed in supine position;
- *Barlow test* is conducted to assess stability of undisplaced hip, by placing the baby in supine position and stabilizing the hips in flexion and adduction. When a posterior force is applied by keeping thumbs medially and fingers externally, an audible click or palpable clunk is felt as femoral head moves out of acetabular cavity. Similar click/clunk also appears after removal of force, due to relocation **(Fig. 23.3B)**.
- *Ortolani test* is used to decide whether CDH is relocatable. When hip is flexed and gradually abducted in supine position, femoral head is lifted anteriorly due to lever action and may enter back into acetabulum with a clunk (*no click*), indicating relocatable hip. Ortolani test is often negative after two months as hips become un-relocatable due to secondary contractures **(Fig. 23.3C)**.
- *Functional defects*, e.g. limping or waddling gait are late features of DDH.

International Hip Dysplasia Registry (IHDR) has recommended following nomenclature for severity spectrum of DDH—(a) dysplasia, (b) subluxable, (c) dislocatable, (d) dislocatable but reducible, and (e) dislocatable and irreducible.

Diagnosis is confirmed on pelvic X-rays in normal and frog-position, though ultrasonography is preferred choice in first six months of life till femoral head is ossified, suggestive of acetabular dysplasia, hip dislocation and abnormal femoral head anatomy. CT/MRI

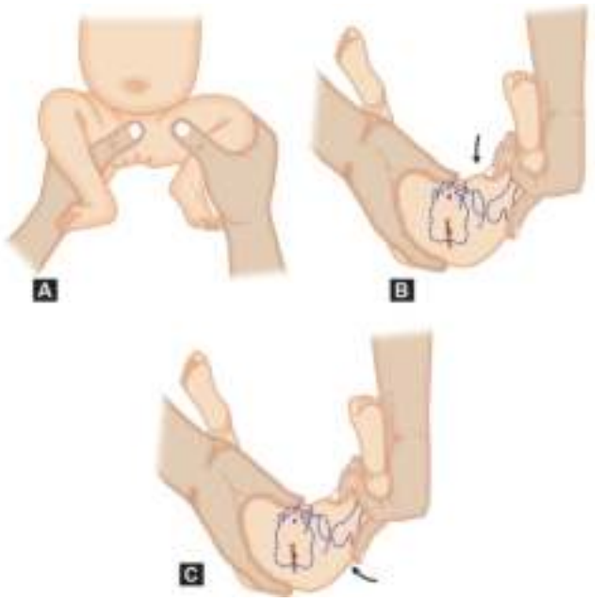

Fig. 23.3: Clinical assessment for DDH in newborns: (A) Limited abduction on affected side; (B) Barlow (dislocation) test; (C) Ortolani (relocation) test.

Fig. 23.4: X-ray: Developmental dysplasia of hip.
Note flat acetabulum on right side with increased joint space and Upward-outward dislocation of femoral head.
(*Courtesy:* Dr S Shrivastava)

may be used in difficult cases. Many cases may not be obvious at birth and need repeated evaluation.

X-ray pelvis (AP view) indicates possibility of DDH, if **(Fig 23.4)**:

- Femoral head is above the *Hilgenreiner's line*, a horizontal line drawn through right and left triradiate cartilage,
- Femoral head is medial to the Perkin's line, a perpendicular line to Hilgenreiner's line through a focus at the lateral side of the acetabulum.
- Disruption in Shenton's line, a smooth arc that connects the femoral neck to the superior margin of the obturator foramen.
- Acetabular index >35% at birth, defined as intersection between Hilgenreiner's line and a line drawn tangential to the lateral ossific margin of the roof of the acetabulum.

Management depends on age of diagnosis and whether hip is still relocatable.

- ***Relocatable hip:*** When diagnosed at birth or in early infancy, hip is often relocatable. These cases require manual relocation followed by splinting (Von-Rosen splint or Pavlik harness) in same position, i.e. flexed and abducted position for 1–2 months, which helps in acetabular development by femoral pressure, normalization of anatomical relationships and strengthening of surrounding ligaments to prevent future dislocations.
- ***Non-relocatable hip,*** usually diagnosed at 6–18 months may require:
  - *Splinting* of hips at >90° flexion and 50–70° abduction, which gradually relocates femoral head into acetabulum within 3–4 weeks. Splinting is highly effective (~90%) in young infants and should continue till normalization of radiological relationship.
  - *Closed reduction* after prior traction over femoral head to relocate it in acetabulum, followed by splinting may be attempted in older children, if simple splinting fails.
  - *Surgical open reduction* is often required in older children >18 months and involves pelvic/femoral osteotomies and realignment.

Outcome depends on the age of diagnosis and efficacy of treatment. Apart from gait or locomotion abnormalities, common complications of untreated CDH include avascular necrosis of femoral head and residual acetabular dysplasia.

Limb-Angulation Disorders

In utero, a fetus rests in a position of complete flexion, with external rotation of femur and internal rotation of leg bones (bowing effect). Consequently, *physiological bowing* (Genu varum) is normal till 18 months of age. Later as the child starts to walk, weight bearing may lead to overcorrection of this angulation with development of *physiological knock knee*, which may persist till 5–6 years.

Genu valgum (Knock-knee), i.e. *inward angulation of knee* due to outward deviation of longitudinal axis of tibia/femur, presents with abnormally divergent legs/ankle and awkward gait, while walking **(Fig. 23.5)**. Severity of knock-knee is assessed by inter-maleollar distance at

Fig. 23.5A and B: **Limb angulation disorders: (A) Bow legs; (B) Knock knee.**

Fig. 23.6: **Congenital talipes equinovarus (CTEV).**

ankle, in straight supine position after approximation of knees, normal being < 8 mm.

Genu valgum is physiological from 18 months to 5 years of age. Severe or pathological genu valgum may be caused by: (a) rickets, (b) neuromuscular disorders, e.g. poliomyelitis or cerebral palsy, and (c) post infective/traumatic damage to *lateral* knee cartilages. Most cases improve spontaneously with further growth and surgical correction is indicated only in progressive defects with functional impairment.

Genu varum (Bow-legs) is the reverse of knock-knee, with *outward angulation of knee joints when ankles are approximated* **(Fig. 23.5)**.

Physiological bow-legs are common in infancy, but severe or pathological bow-legs may be due to: (a) rickets, (b) postural abnormalities (? excess use of round walkers) and (c) post-infective/traumatic damage to *medial* knee cartilages.

Severity of bow-legs may be assessed by measuring inter-knee distance with approximated ankles. Orthotic or surgical correction with osteotomies is required only in very severe cases.

Idiopathic tibia vara (Blount disease) is an important cause of progressive genu varum, specially in obese children, due to idiopathic and abnormal growth of medial aspect of proximal tibial epiphysis.

Genu recurvatum, i.e. *hyperextension of knee* with a tendency to backward dislocation may be due to: (a) developmental ligamental laxity, (b) neuromuscular disorders (polio, cerebral palsy), or (c) post-traumatic/infective injury to tibial tubercle or anterior knee epiphyses. Severe defects with recurrent dislocations may need splinting of knee or operative reduction.

Congenital Talipes Equinovarus (CTEV) or *club foot* is a common foot deformity (1:1000 births), characterized by *plantar flexion of talus, inversion of calcaneus and adduction of forefoot*.

Etiologically, CTEV may be (a) congenital or familial, (b) postural, i.e. abnormal fetal-leg position with increased uterine pressure, e.g. oligohydramnios, or (c) teratologic, e.g. in fetal neuromuscular disorders.

Clinically, it is more common in males (2:1) and with positive family history (? Hereditary). Most cases (2/3rd) are unilateral, more common on right side and present at birth with plantar flexion at ankle (varus) and adduction with internal rotation of foot (equinus), with soles facing inward **(Fig. 23.6)**. Missed or untreated cases in early infancy may develop delayed walking, unsteady gait, callosities and disuse calf atrophy.

Diagnosis is clinical, though radiological evaluation in weight-bearing position is needed before orthopaedic correction, to assess extent of misalignment. CTEV may be detected on prenatal USG by 14–16 weeks.

Management, often termed as ***Ponseti method,*** includes:

- *Conservative treatment* should begin at birth in all cases, with instructing the mother to manipulate the deformity, as frequently as possible. Most cases require: (i) repeated manual correction, followed by taping/malleable splinting, *or* (ii) serial plaster-cast application in corrected posture (revised every 1–2 weeks). After correction, foot may be kept in *Dennis-Brown splint* till walking begins, to prevent re-misalignment.
- *Surgical treatment* is indicated in cases without clinical/radiological correction beyond 3 months of age, involving achilles tenotomy followed by placing a final cast for 3 weeks. After removal of the cast, foot has to be kept in a brace or Dennis-Brown splint-a foot abduction orthosis with two shoes or splints connected by a bar to holds the feet shoulder width apart. This brace needs to worn throughout the day for 3 months followed by only at night time until the child is 4–5 years old. Recurrence is high (80%) in non-compliant cases during brace phase, while it is only 6% incompliant cases.

Talipes calcaneovalgus is milder and opposite variant of club-foot, characterized by dorsi-flexed ankle with abducted and everted forefoot. Most cases are due to abnormal intrauterine position and correct spontaneously by 6–12 months.

Congenital metatarsus adductus or varus (adducted and supinated foot) is more common in first-born infants and young children, due to higher intra-uterine pressure in primigravida. Clinically, foot is convex laterally with prominent base of 5th metatarsal. In long-term, this defect may cause *in-toe* gait and abnormal shoe wear. While passive exercises and corrective shoe-wear are enough in most cases, rigid deformities may require serial plaster-casts or surgical correction.

Adolescent bunions (Hallux valgus deformity), although manifest in adolescence, is usually a result of *congenital malalignment of first metatarsal* with enlarged medial aspect of its head. It is more common in females and those with similar family history. Use of appropriately shaped shoes with wide toe-box is often enough, though orthotic correction or surgery may be needed in selected cases.

Rocker-bottom foot (congenital vertical talus) is an uncommon variant of club foot, due to *abnormal axis of talus,* characterized by hind-foot equinovalgus, convex planter surface and fore-foot abduction with dorsiflexion. It is usually associated with trisomy 13 (Edward syndrome) or arthrogryposis multiplex congenita.

Foot-arch abnormalities: At birth, foot-sole is normally flat due to lax ligaments and medial pad of fat. As the child starts walking, transverse and longitudinal arches develop for better stability, maintained by tarsal and metatarsal bones, planter ligaments and posterior tibial muscles. Most important is the *medial longitudinal arch* that is well formed by 3 years and tends to shift body weight laterally.

Pes planus (Flat foot) denotes absent or poorly formed medial longitudinal arch, leading to abnormal weight bearing on medial rather than the lateral arch.

Etiologically, while physiological till 3 years, pathological flat-foot may be due to—(a) ligamental laxity/injury (*flexible flat-foot*), or (b) tarsal coalition, *i.e.* congenital or post-infective/traumatic fusion of tarsal bones (*rigid-foot*).

Clinically, flexible flatfoot presents in toddlers with unsteady gait with heel in vagus and forefoot in an abducted position but arch is normal in non-weight-bearing position. On the other hand, rigid-foot usually manifests in adolescents with foot/peroneal pain during walking and foot remains flat in weight-bearing as well as non weight-bearing position. Shoe wears out faster on the medial side of the sole.

Tip-toe walking helps to differentiate flexible flatfoot from rigid flatfoot. In a flexible flatfoot, even though the medial longitudinal arch is collapsed during the stance phase; the arch is formed and the heel swings into varus on tip-toe walking but not so in a rigid flatfoot.

Diagnosis is clinical with X-rays in weight-bearing position, which may also demonstrate tarsal coalition.

Treatment is unnecessary for flexible flat-feet except orthotic support and exercises in symptomatic cases. Rigid-foot may require orthotic support or even surgical correction.

Pes cavus, the reverse of pes planus with *exaggerated medial longitudinal arch*, is usually an acquired abnormality during mid-childhood, due to neuromuscular disorders, e.g. Friedreich's ataxia. Conservative treatment is not beneficial and surgical reconstruction of arch is usually necessary.

Developmental upper limb deformities are relatively uncommon than those of lower limbs, though important ones are as follows:

Sprengel deformity denotes *developmental failure of the scapula to descend to its normal location*. Clinically, the scapula is located at an abnormally high position (*winged scapula*), with/without associated features, e.g. webbed neck, low hairline and Klippel-Feil anomaly (Chapter 23.2.3). Severe cases may cause significant cosmetic defect or restricted shoulder mobility, which requires surgical correction.

Nursemaid elbow (Pulled Elbow) denotes *sudden subluxation of radial head with partial entrapment of annular ligament in radiohumeral joint*, usually seen in infants and toddlers due to relatively less bulbous radial head. Subluxation usually begins following jerky longitudinal traction over extended and pronated forearm during play or when the child suddenly falls while hand is held by parents.

Clinically, these cases present with sudden onset of crying and refusal to move upper limb, with hand held in prone position (psuedoparalysis). The arm is held flexed at the elbow with complains of pain at the elbow or the wrist. Baby will allow passive flexion and extension of the elbow but will resist rotations. There are no signs of inflammation around the elbow and X-ray is normal.

Management involves reposition of the radial head and annular ligament by either of the following two methods:

- *Pronation Maneuver* with—(a) holding the arm in semi-prone position with 90° flexion at elbow, (b) simultaneous pronation of forearm and extension of elbow, and (c) flexion of the elbow with forearm pronated; or
- *Flexion-supination maneuver* with—(a) holding the arm in full supination, (b) hyperflexing the elbow with pressure over radial head, to move it inside the annular ligament, when a click is felt over the lateral aspect of elbow.

Once reduced, the pain relief is dramatic with return of functions. No further immobilization is required.

Recurrent subluxation is common in 20–30% cases, till maturity of radial head by 3–4 years. Parents must be counseled not to grab the child by the arm or hand but rather pick them from axilla.

Growing Pains

Growing pains (Recurrent limb pains) are common between 5 and 12 years of age with estimated prevalence of 10–20%.

Etiology is not established but a behavioral component or transient post-activity muscle edema within the limited facial space has been suggested. Other possible reasons include low pain threshold, postural problems, hypermobility of joints, emotional issues or hypovitaminosis D.

Clinically, these cases present with recurrent pain in calves, shin and thigh area, usually in evenings or night. Pains are typically more common after strenuous daytime activity and not associated with local objective signs, e.g. swelling.

Diagnosis is clinical, which may be supported by Peterson criteria, i.e.: (a) intermittent pain once or twice a week, (b) asymptomatic phase between two episodes, (c) short-lasting and poorly-localized limb pains, and (d) *excluding* unilateral limb pain or the nocturnal pain that continues till next morning.

Presence of fever, weight loss, limp between the episodes or local tenderness indicates need for exclusion of other causes, e.g. benign joint hypermobility syndrome, juvenile idiopathic arthritis, complex regional pain syndrome as well as local osteo-articular trauma, infection or malignancy.

Management: No treatment is necessary except assurance, local rubbing/hot fomentation and mild analgesics, e.g. paracetamol. Child may benefit from simple stretching excises of quadriceps, hamstrings and gastrocnemius group of muscles. Gradually, the child outgrows these pains, with no long-term effects.

23.2.3 SPINOTHORACIC DISORDERS

Orthopedic problems of spine and thoracic cage often coexist and may be congenital, developmental or acquired. Apart from following defects, spinothoracic defects are also integral components of many skeletal dysplasias (Chapter 23.4).

Torticollis (Wry neck) is a sign and not a disease, characterized by twisting of neck with head tipped on one side and chin rotated on other side. Presence of torticollis indicates a congenital or acquired deformity of cervical musculature or spine **(Table 23.2)**. Important types of torticollis are as follows:

Congenital torticollis is commonly caused by sternomastoid tumor, i.e. birth trauma to sternocleidomastoid muscle and manifests in early infancy (Ch 12.9.2). However, structural vertebral defects must be excluded before advising neck exercises, which may injure cervical spinal cord.

TABLE 23.2: Causes of torticollis

Congenital
- Birth trauma (Sternocleidomastoid tumor)
- *Vertebral defects:* Klippel-Feil syndrome
- Atlanto-axial joint instability

Acquired:
- Transient torticollis
- Post-traumatic cervical injury
- *Inflammatory:*
  - *Local:* Osteomyelitis, Pott's spine
  - *Adjoining:* Retropharyngeal abscess, adenitis
  - *Systemic:* Rheumatoid arthritis
- *Neurological:*
  - *Central:* Dystonia, posterior fossa tumors
  - *Spinal:* Tumors, syringomyelia
- *Others:* Hysteria, phenothiazine dyskinesia

Klippel-Feil syndrome, i.e. multiple coalitions of cervical vertebrae, is a rare cause of recurrent torticollis, characterized by a triad of: (a) short and webbed neck, (b) low hairline and (c) restricted neck movements. Other congenital defects, e.g. genitourinary malformations, deafness, CHDs and Sprengel deformity (winged scapula) are common.

Transient torticollis is common during viral infections or minor cervical trauma/strain, which improves spontaneously in 2–3 days. A short course of NSAIDs may be used to reduce pain and hasten recovery.

Atlanto-axial joint instability is a rare but potentially life-threatening problem due to: (a) congenital absence of hypoplasia of odontoid process, or (b) ligamental laxity, e.g. in Down syndrome or axial myopathies, or (c) post-traumatic or post-inflammatory degeneration of cervical vertebrae. Normally, flexion/extension movements of neck occur at occipital-C_1 joint, while rotation occurs at C_1–C_2 joint. Neither of these joints are intrinsically stable and depend on surrounding joint capsules and ligaments for stability.

Recurrent torticollis may be first indication of atlanto-axial joint instability and these children are at-risk for sudden death due to spinal compression *or* chronic myelopathy. Detailed neuroimaging is indicated in all suspected cases, followed by preventive advice, e.g. avoidance of contact sports.

Surgical correction with cervical spine fusion is indicated in children with recurrent torticollis with severe instability and/or chronic myelopathy.

Spinal deformities are usually developmental or acquired **(Table 23.3)**, tend to worsen with growth and may lead to significant cosmetic deformities, compressive myelopathy and respiratory insufficiency.

TABLE 23.3: Causes of spinal deformities

- **Idiopathic** scoliosis or kyphosis
- **Congenital** vertebral anomalies
- **Postural:** Leg-length discrepancy
- **Neuromuscular** disorders
  - Central : Cerebral palsy
  - Spinal : Poliomyelitis
  - Vertebral : Pott's spine, trauma, tumors
  - Myopathies : Duchenne muscular dystrophy
- **Miscellaneous:**
  - Postural, arthrogryroposis

Clinically, these deformities manifest either with abnormal spinal curvature, e.g. scoliosis, kyphosis or lordosis; or restricted spinal movements. A normal child has some degree of physiological lordosis in cervical and lumbar region and kyphosis in thoracic and sacral region.

Idiopathic scoliosis is the commonest cause of scoliosis, usually presenting in late childhood and adolescence. Girls are more frequently affected, especially those with similar family history in their mothers (? Genetic).

Clinically, *Adams test* is frequently used to detect subclinical scoliosis, which reveals asymmetry of posterior back contour on forward bending, with elevation towards the convex side of scoliosis.

Diagnosis is confirmed on standing spinal X-rays and *Kobb's method* (angle between long axis of proximal and distal spine at the point of maximum curvature) is used to assess severity of scoliosis. As idiopathic sclerosis rarely leads to compressive myelopathy, neuroimaging is routinely not necessary.

Course: Idiopathic scoliosis is usually progressive during period of skeletal maturation, though the rate of progression depends on various factors, being higher in: (a) early-onset scoliosis, (b) females, specially with premenarchal onset, and (c) severe scoliosis (>30°) at the time of diagnosis.

Management includes long-term brace support, specially till skeletal maturation is complete and/or surgical correction for severe scoliosis (>45°).

Congenital scoliosis is evident at birth or manifests later, caused by: (a) defective vertebral formation, e.g. hemivertebrae, or (b) defective vertebral segmentation, e.g. presence of unsegmented bars. Spinal dysraphism and urogenital disorders are common in these cases.

Progression of deformity and risk of compressive myelopathy depends on the severity of developmental defect, though ~25% cases are non-progressive. Orthotic treatment is of little value, which should be corrected surgically if severe or progressive.

Neuromuscular spinal deformities, due to *static* lesions (cerebral palsy, poliomyelitis) or *progressive* disorders (Duchenne muscular dystrophy) are common in Indian children. Even static pathology may lead to progressive deformities in children due to developing skeletal system.

TABLE 23.4: Causes of back pain

- **Developmental defects**
  - Congenital scoliosis/kyphosis (pre-adolescents)
  - Idiopathic scoliosis/kyphosis (adolescents)
- **Inflammatory disorders**
  - *Local:* Pott's spine, osteomyelitis
  - *Adjoining:* Pyelonephritis, epidural abscess
  - *Systemic:* JRA, spondyloarthropathies
- **Traumatic disorders**
  - *Direct trauma:* Sports injuries, accidents
  - *Mechanical stress:* Gymnasts, heavy schoolbags
  - *Pathological #:* Hemolytic anemia, osteoporosis
- **Neoplastic disorders**
  - Primary/metastatic vertebral tumors
  - Spinal cord tumors
  - Bone marrow malignancies e.g. leukemia
- **Psychological:** Conversion reactions

JRA: Juvenile rheumatoid arthiritis

Management in these cases aims to prevent further deformities and provide maximum functional independence, by external supports (braces), physiotherapy and surgical intervention in selected cases.

Back pain in children is frequently organic, unlike psychological or mechanical back pain in adults and needs detailed evaluation, if persistent.

Common causes of prolonged back pain in Indian children are spinal trauma, developmental defects and inflammatory disorders of spine, each accounting for ~30% of cases **(Table 23.4)**.

Complete physical and neurological evaluation with neuroimaging studies is indicated in children with following danger signals: (a) progressively increasing or persistent back pain, (b) neurological signs, e.g. limb weakness, paresthesias or bladder/bowel dysfunction, (c) constitutional features, e.g. fever and weight loss, and (d) spinal deformities.

Thoracic cage deformities are usually cosmetic, but may lead to significant respiratory insufficiency/failure. Some important abnormalities are as follows:

Pectus carinatum (*Pigeon chest), i.e.* prominent sternum with increased antero-posterior diameter of chest, may be congenital *or* acquired following rickets, recurrent respiratory infections in early childhood, or obstructive airway disorders.

Pectus excavatum (*Funnel chest),* i.e. depressed sternum with decreased antero-posterior diameter of chest, may also be congenital *or* acquired due to causes as for pectus carinatum. Mitral valve prolapse is relatively common in children with congenital pectus excavatum.

Cervical ribs are accidentally diagnosed in children on routine X-rays and rarely symptomatic, though in adults, have been associated with *Raynaud's phenomena*. No treatment is needed.

23.3 LIMPING CHILD

Human gait is cyclic, with two dynamic phases: (a) *stance phase,* when one of the two feet is on ground; and (b) *swing phase,* when legs are advancing forward but with no ground contact.

Development of gait is a function of orthopedic stability and neuromuscular maturation. Early childhood gait is physiologically wide-based, which matures gradually with achievement of normal adult gait by *seven* years.

Limping is a common gait abnormality in children due to orthopedic or neuromuscular causes **(Table 23.5)**, which may be broadly divided into 3 groups:

a. Painful *Antalgic gait* with 'shorter stance' phase on affected side to avoid ground contact with painful limb, usually due to acute inflammatory orthopedic disorders.
b. Painless *Trendelenburg gait* with 'normal stance' phase but a tilt towards the affected site, usually due to neuromuscular disorders (hemiplegic gait) or developmental orthopaedic disorders.
c. *Waddling gait*, due to bilateral disorders, which may be painful or painless.

Evaluation of limp depends on the suspected pathology after physical and neuromuscular examination, although MRI (to visualize unossified joints) and muscle enzymes studies (for myopathies) are useful in cases without obvious etiology.

Some important orthopedic causes of limping or gait abnormalities are as follows:

Leg-length discrepancy may be congenital or acquired, due to orthopedic or neuromuscular disorders in growing child **(Table 23.6)**. Clinically, leg length should be measured from anterior superior iliac spine to medial malleolus, though roentogenographic measurements are more reliable. While mild limb-length discrepancy is common and asymptomatic, severe cases *with* >2 cm difference or associated limp (Trendelenburg gait) require intervention with orthotic/prosthetic support and/or surgical correction (if >5 cm) with limb shortening or lengthening procedures.

TABLE 23.5: Common causes of limping child

Painful limp (Antalgic gait)
- *Infections:* Osteomyelitis, septic arthritis
- *Rheumatic:* Rheumatoid arthritis, transient hip synovitis
- *Trauma:* local sprains, dislocations and fractures
- *Neoplastic:* Bone cysts/tumors, leukemia
- *Congenital:* Tarsal coalition
- *Osteochondroses:* *LCPD, SCFE
- *Painful foot:* skin problems, un-fit shoes

Painless limp (Trendelenburg gait)
- Neuromuscular disorders
  - *Central* : Cerebral palsy
  - *Spinal* : Poliomyelitis
  - *Myopathies* : Duchenne muscular dystrophy
- Developmental orthopedic disorders
  - Developmental dysplasia of hip
  - Leg-length discrepancy

**See* Ch. 23.6

TABLE 23.6: Causes of leg-length discrepancy

Congenital
- Developmental dysplasia of hip (DDH/CDH)
- Hemi-atrophy/-hypertrophy of limbs

Acquired
- *Post-infective:* Osteomyelitis, arthritis
- Post-traumatic malunion or overgrowth
- *Osteochondrosis:* Legg-Calvé-Perthes disease
- *Neuromuscular:* Cerebral palsy, poliomyelitis
- *Others:* Limb tumors, surgery, etc.

Equinus gait (Persistent toe-walking) is uncommon but important indicator of underlying neuromuscular disorders, e.g. cerebral palsy or tendo-Achilles contractures. *Toe-walking is normal till 3 years of age* and some children toe-walk habitually.

In-toe/out-toe walking is a common cause of parental concern, though most of these abnormalities improve with age and no treatment is needed except parental assurance.

- *In-toe walking* is usually caused by developmental torsion defects, e.g. internal femoral torsion (>2 years), internal tibial torsion (<2 years), or congenital talipes equinovarus.
- *Out-toe walking* is usually caused by external tibial version, external femoral version, or congenital talipes equinovalgus.

23.4 SKELETAL DYSPLASIA

Skeletal dysplasia is a heterogeneous group of many genetic disorders, all characterized by *intrinsic defects in formation of cartilage or bone.* Clinical spectrum of these disorders varies from *in utero* lethal defects to very mild disorders, which may remain undetected throughout the life.

Classification: While many classification systems have been proposed for skeletal dysplasias on the basis of genetic, clinical or pathological characteristics, *two* broad types are **(Table 23.7)**:

a. *Chondrodysplasias,* with defective growth of tubular bones and/or spine, e.g. achondroplasia.
b. *Osteodyplasia,* with defective structural modeling or density of bones, due to:
   - Defective collagen, e.g. osteogenesis imperfecta.
   - Defective matrix, e.g. mucopolysaccharidoses.
   - Defective bone resorption, e.g. osteopetrosis.

Chondrodysplasias are characterized by genetic defects in enchondral bone formation and growth.

TABLE 23.7: Common skeletal dysplasias

A. Chrondodysplasia

Short-limb skeletal dysplasias

– *Predominantly rhizomelic*
  Achondroplasia
  Hypochondroplasia
  Thanatophoric dysplasia*
  Metatrophic dysplasia
  Chondrodysplasia punctata
– *Predominantly mesomelic*
  Camptomelic dysplasia*
  Mesomelic dysplasia
  Short-limb polydactyly syndromes*
– *Predominantly acromelic*
  Asphyxiating thoracic dystrophy*
  Ellis-van Creveld syndrome
  Cartilage-hair hypoplasia
  Pyknodysostosis
  Diastrophic dysplasia
  Multiple epiphyseal dysplasia

Short-trunk skeletal dysplasias

– With mild micromelia
  Spondyloepiphyseal dysplasia
  Mucopolysaccharoidosis
– With moderate/severe micromelia
  Achondrogenesis**
  Kniest syndrome
  Spondylometaphyseal dysplasia

Osteodysplasia

Osteogenesis imperfecta**
Osteopetrosis

*lethal at birth or in neonatal period
**some types are lethal at birth

Disproportionate short stature is the hallmark of these disorders, which may be divided into: (a) *short-limb dwarfism* with disproportionate shortening of limbs as compared to trunk, e.g. achondroplasia, and (b) *short-trunk dwarfism*, e.g. spondyloepiphyseal dysplasias.

Short-limb chondrodysplasias are further subclassified as those with: (a) *Rhizomelia,* i.e. predominant shortening of proximal limb segments like upper arms and thighs, (b) *Mesomelia,* i.e. predominant shortening of middle segments like forearms and legs and (c) *Acromelia,* i.e. predominant shortening of distal segments like hands and feet.

Osteodysplasias are characterized by genetic defects in modeling of bones, leading to altered bone density, including two broad subtypes;

a. Disorders with decreased bone density, e.g. osteogenesis imperfecta; and
b. Disorders with increased bone density, e.g. osteopetrosis or pyknodysostosis.

Diagnostic evaluation of skeletal dysplasia is largely based on clinical and radiological features. Important steps in approach to a suspected case are as follows:

a. *Demonstration of short stature* on anthropometric evaluation, though many mild cases may be normal at birth and short stature becomes apparent only in late childhood.

b. *Assessment of body proportions*: Disproportionate shortening is best assessed by measuring upper-segment : lower-segment ratio (US:LS ratio). Normal US:LS ratio varies with age, being-1.7:1 at birth, 1.3:1 at 3 years and 1:1 at 7 years. Although criteria for individual limb segments are available, Rhizo-/Meso-/Acro-melia is usually identified by clinical appearance.

c. *Clinical features*, e.g. age of presentation, family history and presence of coexisting non-skeletal defects provide important clues for detection and classification of diagnosis.

d. *Radiological evaluation* is often diagnostic and requires complete skeletogram including limb, spine, thorax and skull X-rays in different views.

e. *Molecular diagnosis* with genetic studies are preferable whenever possible, to decide about the future risks of recurrence.

f. *Other laboratory investigations* are of a little use, except in osteogenesis imperfecta or MPS.

Some important skeletal dysplasia are as follows:

Achondroplasia: Achondroplasia is the commonest skeletal dysplasia (~1:15,000), clinically characterized by typical short-limb dwarfism and craniofacial abnormalities, apart from other features.

Etiology: Although transmitted as an autosomal dominant disorder, most cases arise from a new mutation in normal parents at *FGFR3 gene* codon 380, which governs the rate of enchondral bone formation.

Clinically, skeletal manifestations are obvious at birth, while secondary neurological features appear at a later age. Important features include:

- *Rhizomelic, short-limb, short stature,* i.e. normal sized trunk but relatively shorter extremities, specially in proximal parts, e.g. upper arms and thighs. Hands are broad and short, with a *trident-like* arrangement of fingers. Bowing of legs is common **(Fig. 23.7A)**
- *Craniofacial abnormalities*, e.g. large head, prominent forehead, depressed nasal bridge, hypoplastic maxilla with relative prognathism. Dental malocclusion is common.
- *Hypotonia* is common in earlier years leading to: (i) delayed early motor development, (ii) prominent lumbar gibbus in infancy, gradually replaced by lumbar lordosis as child starts to walk, and (iii) hyperextensible joints, except elbow, where movements may be restricted.
- *Neurological complications* may develop at any age due to skeletal malformations and include: (i) *hydrocephalus* due to platybasia-narrow base of the skull, (ii) *compressive myelopathy* due to spinal canal stenosis at

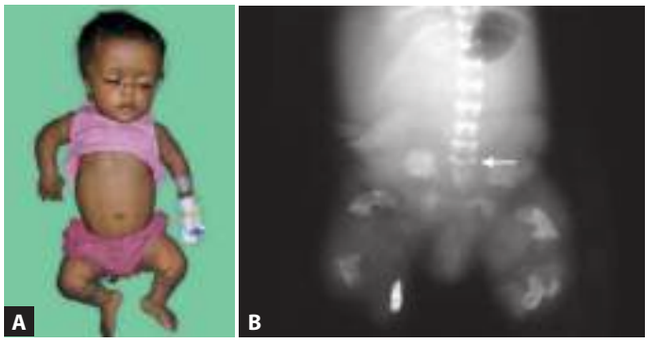

Fig. 23.7A and B: Achondroplasia (Clinical): (A) Appearance with short limbs; (B) Short vertebral pedicles with wedging.

cervical region (common in infants) or lumbar region (common in adolescents). Intelligence is normal, unless affected by hydrocephalus.

- *Recurrent otitis media* is common due to ear canal deformities, leading to conductive hearing loss in older children.

Diagnosis rests on clinical appearance simulating *'circus dwarfs'*, anthropometry (short stature with higher US:LS ratio) and radiological evaluation. Important radiological signs include:

- Rhizomelic shortening of long bones with irregular, flared metaphyses (V-shaped or *circumflex sign*).
- Large calvarium with narrow base of skull and shorter facial bones
- Short vertebral pedicles with reducing inter-pedicular distance from L_1 to L_5, (in contrast to normal caudal widening). Lower thoracic or upper lumber vertebrae may show anterior *tonguing/wedging* and posterior *scalloping* **(Fig. 23.7B)**.
- Short and broad iliac wings with horizontal acetabular roof.

Management aims to: (a) treat neurological complications, e.g. hydrocephalus or spinal canal stenosis, (b) correct orthopedic deformities, and (c) provide social and psychological support.

Prognosis: Life span is normal in absence of neurological complications. Post-marriage, risk of achondroplasia in offsprings is ~25% for having homozygous disease and ~50% for being heterozygous carriers. Prenatal diagnosis is possible for homozygous disease.

Hypochondroplasia is a milder variant of achondroplasia, where infant is stocky and muscular in appearance and short stature is not evident until late childhood. Craniofacial deformities are minimum except frontal bossing, and skeletal deformities are limited to some bowing of legs. Some cases have FGFR3 gene mutation at codon 540.

Thanatophoric dwarfism is the most severe skeletal dysplasia with extremely short limbs, small and pear-shaped chest and severe radiological changes at birth with clover-leaf skull deformity (*Kleeblatts chädel skull*) in some cases. Most cases are stillbirths or die in neonatal period due to respiratory distress, owing to thoracic deformity. Some cases have *FGFR3 gene mutation at codon 650*.

Spondyloepiphyseal dysplasia (SED) is a heterogeneous group of uncommon chondrodysplasias, all characterized by *short-trunk dwarfism* due to abnormal development of vertebral bodies. This group includes many disorders of variable severity, ranging from lethal variants in neonatal period, e.g. *achondrogenesis (type II)* or *hypochondrogenesis*, to milder variants, e.g. *SED congenita*, *SED tarda* or *Kneist dysplasia*.

SED congenita, prototype of this group, manifests at birth or in infancy, with short trunk and neck, barrel shaped chest, relative rhizomelia, hypotonia with waddling gait and flattened vertebrae with delayed ossification on spinal X-rays. Disproportionate short stature worsens with age and many cases die in childhood due to respiratory compromise *or* develop neurological complications due to spinal deformities.

Osteogenesis imperfecta (OI) or *Brittle-bone disease*, is the commonest osteodysplasia (~1:20,000), characterized by a genetic defect in skeletal modelling with generalized decrease in bone density.

Etiology: OI is an autosomal dominant disorder, with primary defect in synthesis of type I collagen-main component of the extracellular matrix of bone and skin.

Clinical spectrum: Easy fracturability of bones with consequent bony deformities is the hallmark of OI, though severity may vary from early lethal forms to very mild disease, as follows *(Sillence classification):*

Type I (mild) is characterized by a triad of: (a) recurrent fractures, (b) blue sclera and (c) early deafness in ~30–60%. Similar family history is often present. Fractures begin in infancy or early childhood (not *in utero*, d/d other types), usually after trivial trauma and frequency reduces after puberty. Dental abnormalities, easy skin bruising and joint laxity is also common.

Type II (perinatally lethal) presents with multiple *in utero* fractures with severe deformities at birth, e.g. bowing of extremities, small beaded thorax due to rib fractures, large head with wide fontanels and dark blue sclera. Most cases are stillborn or die in early infancy.

Type III (progressive deforming) presents with severe and progressive deformities after repeated postnatal fractures *since* birth, though intrauterine fractures may occur. Short stature, scoliosis with spinal compression and chest deformities are common. Sclera may be blue to white.

Type IV (moderately severe) is an intermediate variant between type III and I as *in utero* fractures may occur (d/d type I) but postnatal fractures are more common after ambulation (d/d type III). Moderate bowing of long

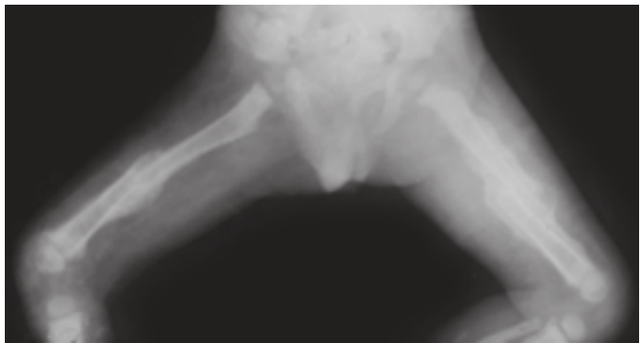

Fig. 23.8: **Osteogenesis imperfecta: Multiple fractures.**

bones with short stature is prominent feature in these cases, and fracture rate reduces after puberty. Sclera may be blue or white.

Type V and VI are rare cases similar to type IV disease but with different histology. A few cases of autosomal recessive type VII and VIII have been also reported.

Both, type I and IV disease, are also sub-classified as A and B, depending on the absence *or* presence of dental abnormalities (*Dentinogenesis imperfecta)*, respectively.

Diagnosis must be suspected in any child with recurrent non-pathogenic fractures **(Fig. 23.8)** and confirmed by molecular studies or collagen biochemistry on skin biopsy (reduced type I collagen with altered type III:I collagen ratio on protein electrophoresis). *Prenatal diagnosis* is possible in cases with family history on chorionic villous biopsy as early as at 12 week. Presence of intraunterine fractures on USG may be detected as early as at 16th weeks, suggesting severe disease.

D/D of OI includes other causes of recurrent pathological fractures, e.g. battered child, hemolytic anemia, osteoporosis/penia, hypophosphatasia, etc.

Management is non-specific and aims to reduce the frequency of fractures and deformities by: (a) avoidance of strenuous activities or sports, (b) early treatment of fractures, (c) surgical correction of deformities, (d) orthotic support and physiotherapy.

Drugs, e.g. calcium or fluoride supplements are not effective, though growth hormone therapy *or* monthly IV biophosphonate infusions have been found of some benefit. Role of bone marrow transplant in severe cases is experimental.

Prognosis: Type I and IV may have normal life span but with disability, while Type II and III die in infancy or early childhood, respectively.

Common complications in survivors are: (a) functional deformities, (b) recurrent pneumonia due to thoracic deformities, (c) neurological complications, e.g. basilar invagination, hydrocephalus, etc. Recurrence risk in next sibling is 5–50% depending on the genotype.

Osteopetrosis (Marble-bone disease) is a rare but important disorder of *defective bone resorption,* leading

Fig. 23.9: **Osteopetrosis: Bone in bone appearance.**

to increased bone density and sclerosis with *bone-in-bone appearance* on X-rays **(Fig. 23.9)**.

These cases present with: (a) failure to thrive, (b) severe anemia due to encroachment of marrow spaces, (c) hepatosplenomegaly and macrocephaly due to extramedullary erythropoiesis, (d) pathological fractures due to defective bone architecture, and (e) blindness, deafness or facial palsy, due to narrowing of cranial nerve exit-foramens.

More severely affected children have an autosomal recessive disease (usually TCIRG1 mutation) and die in infancy, while less severe autosomal dominant cases may survive till late childhood. Treatment is symptomatic though bone marrow transplant is useful in some cases.

23.5 BONE AND JOINT INFECTIONS

Orthopedic infections are important causes of long-term disability in children, due to involvement of *growing* skeleton. Infection is usually acquired via hematogenous route and frequently involve joints and bones *together* due to common source, immature epiphyseal plate and *intra-articular* metaphyses at many joints.

23.5.1 ACUTE OSTEOMYELITIS

Osteomyelitis in children primarily involves long bones of the lower or upper limbs. It is more common in males and ~1/3 cases occur <2 years of age.

Etiology: *Staph. aureus* is the commonest causative organism for acute osteomyelitis, followed by Streptococci, Pneumococci and *H. influenzae*. Gram negative or anaerobic osteomyelitis is common in posttraumatic infections. Osteomyelitis in sickle cell anemia is usually due to salmonella and *H. influenzae*.

Pathogenesis: Infection is usually acquired via *hematogenous route* following septicemia from a distant focus, or *direct inoculation* after neighboring injuries/surgeries.

Metaphyses of long bones are commonest sites for localization of blood-borne infection, due to typical vascular anatomy, i.e. sinusoidal network with sluggish blood flow. From here, infection may spread to diaphysis and subperiosteal space through Haversian system and Volkmann canals. Although epiphyseal plate limit extension of infection into joint space, co-arthritis is common in infants due to criss-crossing capillaries.

Chronic osteomyelitis is pathologically characterized by formation of abscess (*Brodie's abscess*), sequestrum (dead bone tissue), sub-periosteal involucrum (reparative bone tissue) and occasionally, sinus tracts to discharge the pus on skin surface. Weakened bone at the site of these changes is susceptible for pathological fractures.

Clinically, early osteomyelitis may be asymptomatic till the infection extends beyond metaphysis, while an established case presents with: (a) local inflammation, e.g. pain, tenderness, swelling and restricted movements of affected site, and (b) constitutional features, e.g. fever.

Constitutional signs are minimal in chronic osteomyelitis, which usually presents with chronic discharging sinuses and pathological fractures at the site of lesion.

Diagnosis: Radio nucleotide bone scan (^{99m}Tc) or MRI of the suspected site is the best investigation for diagnosis of early osteomyelitis, as X-ray changes appear only after 7–10 days.

On X-rays, *periosteal elevation over metaphysis* is the earliest sign, followed by irregularity of cortex, abnormal diaphyseal densities (sequestrum), subperiosteal bone formation (involucrum) with sequestrum formation in more chronic cases **(Fig. 23.10)**.

Ultrasonography to exclude co-existing arthritis and Blood/pus *cultures* for specific antibacterial therapy are indicated in all cases, though ~1/3rd cases are sterile at the time of diagnosis.

Fig. 23.10: Osteomyelitis: Arrows indicate sequestrum.

Treatment of osteomyelitis includes:

a. Antibiotics: Vancomycin (or Cloxacillin) with a third generation cephalosporin is the drug of choice for empirical therapy till culture reports. Vancomycin is preferred in settings with high MRSA resistance. Clindamycin may be used in cases allergic to betalactam drugs. It is also effective against anaerobic infections common after penetrating injuries or compound fractures. Initial therapy is essentially intravenous, which may be switched to oral antibiotics after 7–10 days in good responders and continued for minimum 14–21 days or till resolution.

b. Surgical intervention is indicated in cases with arthritis (pus drainage) or chronic osteomyelitis (curettage and removal of sequestrum).

c. Limb immobilization (splinting/cast) is useful in select cases to reduce pain and restrict movements, which may facilitate spread of infection or cause pathological fractures. However, passive physiotherapy should begin as soon as pain subsides.

Outcome depends on severity/duration of osteomyelitis and promptness of therapy. Chronic osteomyelitis may lead to pathological fractures, deformities and limb shortening.

23.5.2 SEPTIC ARTHRITIS

Septic arthritis is usually monoarticular and involves knee or hip in ~75% cases. In children, it is more common than osteomyelitis, with higher risk of residual sequelae.

Etiology: *Staph. aureus* is the commonest cause of septic arthritis, followed by *H. influenzae,* streptococci and pneumococci. Opportunistic infections, e.g. Candida or *Staph. epidermidis* may cause arthritis in newborns *or* children with indwelling catheters.

Pathogenesis: Joint Infection is usually acquired via *hematogenous route* from a distant focus or adjoining infected metaphysis (osteomyelitis), though direct inoculation may occur after penetrating injuries or surgical interventions, e.g. arthroscopy/aspiration.

Pathological sequence in septic arthritis includes: (i) synovitis and exudation, (ii) pus collection in joint space, (iii) destruction of articular cartilage, and (iv) spread to adjoining bones or extra-articular tissues.

Clinically, septic arthritis begins with acute joint pain and restricted movements (pseudoparalysis), followed by local swelling, heat and constitutional signs, e.g. fever.

Diagnosis: Early diagnosis requires USG of suspected joint, followed by joint aspiration for pus culture.

Routine X-rays are normal in first week, while later abnormalities may include: (i) widening of joint space, (ii) synovial capsular swelling/thickening, (iii) erosion/destruction of cartilage and (iv) edema or displacement of surrounding tissues.

TABLE 23.8: Causes of acute arthritis

- *Infections:* Septic arthritis, tubercular arthritis
- Reactive arthritis
- Post-traumatic
- Malignancy e.g. leukemia
- *Hemarthrosis:* Hemophilia, scurvy
- *Vasculitis syndromes:* Henoch-Schönlein purpura
- *Rheumatoid disorders:* JRA, SLE

Radio nucleotide bone scan may be used to exclude associated osteomyelitis.

D/D of septic arthritis includes other causes of acute monoarticular arthritis **(Table 23.8)**, osteomyelitis and soft tissue injuries/infections. Recurrent septic arthritis or poor response to antibiotics indicates possibility of tubercular arthritis or rheumatoid disorders.

Treatment of septic arthritis includes:

- Empirical *antibacterial therapy,* as for osteomyelitis, followed by specific therapy after pus culture reports.
- *Joint aspiration* under USG guidance, in cases with large effusions. *Surgical intervention, i.e.* arthrotomy and joint-toilet with normal saline is indicated in: (a) severe hip joint arthritis or arthritis after penetrating injuries, (b) rapid refilling of joint space despite repeated aspirations, (c) presence of pus in subperiosteal/metaphyseal space, and (d) poor response to antibiotics.
- *Symptomatic treatment* to reduce pain, e.g. analgesics and limb immobilization. However, physiotherapy should being as soon as the pain subsides.

Outcome depends on severity, duration and type of joint involvement, with potential risk of long-term disability in all cases. Hip arthritis carries worst functional prognosis, due to frequently impaired blood supply for the head of femur.

Some other important causes of acute arthritis, not discussed elsewhere, are as follows:

Reactive arthritis (Post-infectious arthritis) is a common, transient and self-limiting arthritis, following or associated with many extra-articular infections, e.g. (a) exanthematous viral illnesses, e.g. measles,varicella, (b) respiratory viral or mycoplasmal infections, (c) enteric infections, e.g. shigellosis, and (d) chlamydial urinary tract infections.

Pathogenesis is exactly not known, probably relates to autoimmune response involving cross-reactive T-lymphocytes or deposition of immune-complexes in joints. A genetic predisposition with presence of HLAB27 is known in chronic reactive arthritis.

Clinically, these cases present during or within 2–4 weeks of causative infection, with arthralgia/arthritis of one or more large joints. Most cases recover spontaneously within few days and persistent arthritis beyond 6 weeks is rare, except in HLA-B27 positive children. *Enthesitis*, i.e. pain and tenderness at the site of tendon attachments is common. Some cases of reactive arthritis are associated with extra-articular manifestations, e.g. urethritis and conjunctivitis (Reiter syndrome), dermatitis (Hepatitis B), pancytopenia (parvoviral infections), etc.

Diagnosis rests on exclusion of other causes, with transient course and normal X-rays. Acute phase reactants, e.g. ESR, are usually normal.

Treatment is non-specific, except symptomatic pain relief with anti-inflammatory agents till spontaneous recovery. However, cases with prolonged symptoms should be followed up to detect late-abnormalities, e.g. inflammatory bowel disease or uveitis.

Transient synovitis of hip is a common cause of acute painful limping in children. Although exact pathogenesis is uncertain, preceding viral infection is present in ~70% cases. Most cases occur in 3–8 years age group with male preponderance.

Diagnosis is based on exclusion of other causes of hip pain, e.g. trauma or arthritis on the basis of: (a) absence of fever and leukocytosis, (b) minimal restriction of movements, and (c) normal X-rays except mild joint effusion. Bone scan and joint aspirates are normal while synovial biopsy may reveal non-specific inflammation.

Management: Bed rest, avoidance of weight bearing and NSAIDs are usually enough for symptomatic relief in this self-limiting condition, while persistent symptoms demand evaluation for more serious disorders.

23.5.3 OSTEOARTICULAR TUBERCULOSIS

Skeletal tuberculosis is a late lesion in natural history of tuberculosis, uncommon before 4–5 years of age.

Infection is usually acquired via hematogenous route (disseminated tuberculosis) from pulmonary focus and remains dormant for many years before manifestations. Trauma, even trivial, is an important preceding factor to facilitate localization of bone infection or progression to disease, due to local vascular injury and inflammation.

Pathologically, these lesions are characterized by caseating necrosis, granuloma, bone destruction and ultimately, cold-abscess formation that may trickle to neighboring tissues or through skin (sinus formation).

Common sites of skeletal tuberculosis are: (a) spine (*Pott's spine*), (b) short bones of hands/feet (tubercular dactylitis) and (c) large joints of lower limbs, e.g. hip.

Pott's spine is the commonest osteoarticular tuberculosis, which primarily involves thoracolumbar spine due to its excessive motility, curvature and maximum stress/strain injury. Apart from hematogenous route, infection may also reach the spine by lymphatics from paravertebral nodes.

Pathogenesis: Commonest site for initial localization of infection in Pott's spine is: (a) metaphyseal region

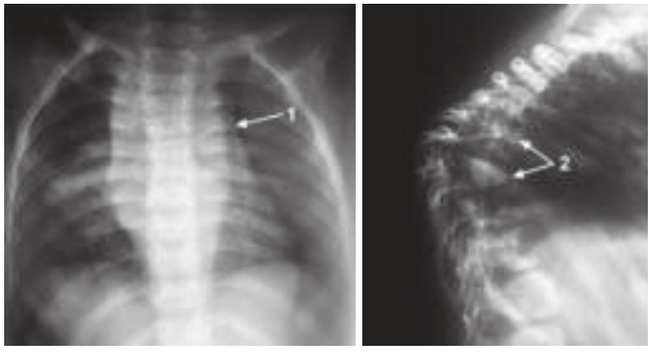

Fig. 23.11: Pott's spine: Arrows indicate paravertebral abscess[1] and collpased vertebrae[2]
(*Courtesy:* Dr S Shrivastava)

of vertebrae, adjoining intervertebral disc, followed by (b) central part of body, (c) anterior surface under the anterior longitudinal ligament or rarely, (d) from posterior elements, e.g. lamina or spinous processes. Local lesion may remain dormant *or* progresses into cold abscess, vertebral destruction and collapse.

Clinically, these cases may present with: (a) localized spinal tenderness or pain during movements, (b) spinal deformity, i.e. kyphosis due to vertebral collapse, (c) signs of compressive myelopathy (20–30%), and/or (d) cold abscess, which may travel along the tissue planes to manifest at distant sites, e.g. psoas abscess, chest-wall abscess, etc. Constitutional symptoms may be present.

Diagnosis must be suspected on clinical grounds and radiological signs, e.g. (a) reduced intervertebral disc spaces, (b) destruction/collapse of vertebrae, and (c) paravertebral shadows of cold abscesses **(Fig. 23.11)** apart from collaborative evidences for tubercular etiology, e.g. positive chest X-ray, tuberculin test and raised ESR. However, X-rays are unreliable in early disease and CT/MRI is necessary in most cases for confirmation as well as to assess the severity of cord compression.

CT guided biopsy should be attempted in all cases for etiological confirmation for histopathology as well as detection of AFB on staining, culture or CBNAAT, as the gold standard.

Treatment of Pott's spine includes:

- Specific antitubercular therapy including 2HRZE + 10HRZ in drug-sensitive cases, to be modified in resistant cases (Ch 10.13).
- Spinal immobilization in POP jacket/brace during initial 2–3 months, in cases with spinal deformity.
- Drainage of cold abscess, if large or compressing the vital organs.
- General supportive and symptomatic therapy.

Surgery may be indicated in cases with—(a) progressive neurological deficit, (b) paraplegia of recent onset or severe paraplegia, (c) persistent pain with spinal instability, (d) severe or progressive spinal deformity.

Tuberculosis of hip is commonest form of tubercular arthritis, followed by knee involvement, due to weight-bearing nature of these joints. Acquired via hematogenous route, infection usually spreads from local osteomyelitis of acetabular roof, femoral head, neck of femur or greater trochanter.

Clinically, these children present with: (a) restricted movements, (b) joint pain on sudden movements (*night cry*), and (c) limb-length discrepancy due to protective muscular spasm (*apparent shortening*), joint effusion (*lengthening*) or articular destruction (*true shortening*). Acetabular destruction may lead to upward displacement of femoral head (*wandering acetabulum*). Cold abscesses from hip usually form in inguinal region.

Diagnosis rests on radiological signs: (a) reduced or increased joint space, (b) destruction of articular cartilages, and (c) surrounding osteoporosis. USG or MRI is preferable for early diagnosis and to delineate extent of joint damage. Diagnosis must be confirmed by joint aspiration or synovial biopsy for microbiological confirmation including drug sensitivity profile as well as exclusion of septic arthritis or transient synovitis of hip.

Treatment: Apart from specific antitubercular therapy (Ch 10.13), orthopedic management includes traction immobilization for 4–6 weeks, followed by gradual mobilization to retain hip function.

In severe cases with cartilaginous destruction, normal mobilization is almost impossible and orthopaedic management aims to achieve a fixed joint in functionally optimal position by prolonged traction/POP immobilization for 4–6 months *(Ankylosis)*, or surgical fusion of joint *(Arthrodesis)*.

Overall functional prognosis is poor despite best treatment, unless hip transplant is possible.

Tubercular dactylitis presents as painful/tender, spindle-shaped swelling of affected phalynx (*spina ventosa*) with/without discharging sinus. X-ray of affected finger/toe reveals a lytic lesion with minimal sclerosis or new bone formation. Apart from specific antitubercular therapy, immobilization of finger for 4–6 weeks may be helpful. Surgical curettage with bone grafting is necessary in large lesions.

23.6 OSTEOCHONDROSES

Osteochondroses (idiopathic avascular necrosis) are non-infective, non-inflammatory disorders of any bone, *due to focal ischemic necrosis of growing epiphyses or ossification centers.* The exact cause for vascular insult is not clear, but probably relates to traction, stress fractures or compression injury.

Clinically, these disorders are common in adolescents (except Legg-Calve-Perthes disease) and present with localized, constant or intermittent pain at the site of affection, without signs of inflammation. Almost all

osteochondroses are self-limiting and need to be treated symptomatically with temporary immobilization.

While osteochondroses involving almost every long bone or spine have been described, some common lesions are as follows:

Legg-Calve-Perthes disease (LCPD) represents *avascular necrosis of femoral capital epiphysis* due to unknown etiology, probably related to some hypercoagulation defect.

More common in males (5:1) and pre-adolescents (2–12 years), LCPD presents with mild intermittent pain in anterior thigh or painless limping gait. Diagnosis is radiological, to demonstrate shape and size of femoral head and surrounding osteoarthritis.

Most cases recover spontaneously and need only symptomatic treatment. However, severe, non-resolving cases may need limb immobilization in abduction or surgical correction.

Slipped capital femoral epiphysis (SCFE) is predominantly a disorder of obese or rapidly-growing adolescents, probably related to hormonal changes. Endocrinal defects, e.g. hypothyroidism or growth hormone deficiency are common in rare pre-adolescent cases.

Clinical presentation depends on severity of slippage. *Acute SCFE* presents with severe hip pain during attempted motion, while *chronic cases* develop antalgic (painful) gait and external rotation of affected leg.

Diagnosis is radiological with: (a) widening of epiphysis during pre-slip phase, (b) anterior rotation of femoral neck, and (c) slipped capital femoral epiphysis outside the acetabulum.

Treatment aims to prevent further slippage, by surgical closure of CFE, i.e. epiphysiodesis. Untreated cases may develop complications like osteonecrosis (avascular necrosis of head) and chondrolysis (degeneration of articular cartilage of hip).

Osteochondritis dissecans, i.e. s*eparation of a part of articular cartilage and subchondral bone* at certain joints, e.g. knee, ankle and elbow, is usually seen in late adolescence.

Clinically, these cases present with recurrent pain, swelling of affected joint along with its *locking* in flexed position. Frequently, the loose part may be palpable with changing position (*Joint mouse*).

Diagnosis is based on X-ray or arthroscopy to detect loose segment. While partially separated part may be re-fixed, completely loose segment needs surgical removal to prevent further articular trauma.

Scheuermann's disease, i.e. *osteochondrosis of vertebral bodies* is the third commonest cause of spinal deformities in adolescents, after infections and idiopathic scoliosis. Mostly seen in early adolescence, these cases present with thoracic kyphosis and typical tightening of hamstrings. X-ray reveals wedging of affected vertebrae. Correct body posture, exercises and orthotic supports are usually enough to improve the posture and surgery is rarely indicated.

Osgood-Schlatter's disease, i.e. *osteochondritis of apophysis of tibial tubercle*, presents with knee pain without other signs of inflammation, usually in adolescent boys. X-ray may reveal hyperdensity and/or fragmentation of upper tibial apophysis. Treatment is symptomatic, with spontaneous recovery in 1–2 years.

Sever disease, *i.e. osteochondrosis of calcaneum* presents with heel pain and tenderness in early adolescence (10–15 years). It appears to be related to repeated stress at the site of tendoachilles insertion. Treatment is symptomatic, with rest and POP cast for 3–4 weeks.

Panner's disease, *i.e. osteochondrosis of capitellum*, is most common in adolescence, predominantly related to sport-injury, e.g. ball-throwing. It presents with local elbow pain, crepitation and restricted pronation-supination movements. Diagnosis is based on X-ray or MRI and treatment is conservative with restriction of activities. Surgical intervention is indicated only if overlying cartilage is disrupted or fragmented.

23.7 BONE MASSES AND TUMORS

Presence of a hard bony mass is a common orthopaedic problem in children **(Table 23.9)**. While most of them are benign hamartomas or reparative bony overgrowth (reactive bone lesions), differentiation from malignant tumors is essential. Conversely, many bone tumors present like an inflammatory bone disease, e.g. osteomyelitis.

Benign masses are usually slow-growing and non-tender, more common in adolescents. On the other hand, malignant tumors may develop at any age, grow rapidly and frequently associated with constitutional features. Diagnosis rests on radiological findings and biopsy.

TABLE 23.9: Common bone masses in children

- **Hamartomas**
  - Osteochondroma
  - Enchondroma
- **Reactive masses**
  - Mal-united fractures
  - Osteoid osteoma
  - Benign osteoblastoma
- **Bone cysts**
  - Ganglions
  - Solitary bone cyst
  - Aneurysmal cysts
- **Primary bone tumors**
  - *Osteogenic:* Osteosarcoma
  - *Chondrogenic:* Chondroblastoma/sarcoma
  - *Connective tissue:* Fibrosarcoma
  - *Myelogenic:* Ewing's tumor, lymphoma
  - Osteoclastoma (Giant bone tumor)
- **Secondary (metastatic) tumors**

Fig. 23.12: **Osteochondroma.**

Some important non-malignant bony masses are discussed here. For malignant tumors, *see* Ch 20.7.

Osteochondroma **(Solitary exostosis)** is the commonest tumor-like bony swelling in early adolescence, arising from metaphyseal ends of long bones, specially near knee and elbow. Pathologically, it denotes transverse overgrowth (hamartoma) of cartilaginous cells from epiphyseal plate.

Apart from hard bony swelling, these cases may develop local pain, restricted movements, pathological fractures and adjoining nerve/vessel compression. Malignancy is rare. X-ray reveals continuity between cortex and medulla of exostosis and main bone. Small asymptomatic lesions need no treatment while larger ones may be excised **(Fig. 23.12)**.

Enchondroma are benign cartilaginous overgrowths from short long bones, e.g. metacarpals and phalanges. Although usually asymptomatic, some lesions may develop pathological fractures. *Ollier disease* is a developmental disorder with generalized enchondromatosis.

Osteoid osteoma is a reactive bone lesion, mostly involving cortical areas of femur, tibia and vertebrae. Clinically, these lesions are usually seen beyond 10 years, more common in males and presents with localized pain and tumor-like mass. vertebral lesions may cause spinal cord/root compression. Radiologically, these lesions appear as cystic lesions with an expanding osteolytic lesion and thin cortex of sclerosis. Treatment includes excision/curettage of lesion.

Solitary bone cysts (*Unicameral bone cysts*) are true cystic lesions at the ends of long bones, usually involving proximal ends of humerus and femur. Clinically, these lesions may be asymptomatic or present with pathological fractures. Diagnosis is based on X-ray and aspiration of the cyst aspiration which may be hemorrhagic. Small cysts heal themselves, while larger ones need surgical curettage and bone grafting. Intralesional methylprednisolone acetate injection is known to heal many lesions.

Aneurysmal bone cyst is solitary rapidly progressive cystic lesion of long bones and vertebrae, probably representing an arteriovenous malformation after trauma or neoplasia. These lesions are rare in childhood, usually presenting as painful swellings in young adults. Along with X-rays, local biopsy is diagnostic, revealing honeycomb of blood-filled cavities. Excision/curettage with grafting is curative though recurrence is common.

Ganglion is a synovial fluid-filled cyst around the wrist, usually on the dorsal aspect. It denotes a defects in the joint capsule, which allows herniation of the synovium to cause rupture and fluid leakage in soft tissues, followed by reactive fibrosis to wall-off the leak.

In children, most ganglions disappear spontaneously over time and aspiration is indicated only if it is painful, sufficiently large or interferes with normal tendon function. Surgical excision of lesion and tract to the joint space is curative.

Popliteal (Baker) cyst is commonly seen in mid-childhood due to distension of gastrocnemius and semimembranosus bursa along the postero-medial aspect of knee by synovial fluid from tendon sheaths. Knee X-ray is normal and diagnosis may be confirmed on USG or aspiration. Most cysts resolve spontaneously after many years and surgery is very rarely indicated.

23.8 FRACTURES IN CHILDHOOD

Pediatric fractures differ from adult fractures on following counts:

1. Tendency for angular/green-stick fractures due to relatively pliable bones,
2. Less risk of displacement due to thicker and stronger periosteum, though it also impedes closed reduction,
3. Rapid healing due to metabolically active periosteum,
4. Higher capacity for remodeling that obviates the need for strict re-alignment, and
5. Tendency for overgrowth deformities in affected limbs due to excessive callous formation.

Types: Pediatric fractures may be broadly divided into non-epiphyseal and epiphyseal fractures.

Non-epiphyseal fractures are more common and include many variants, e.g. (a) complete fractures involving both sides of bone, (b) buckle or torus fractures due to sudden bone compression, (c) Green-stick fractures with angulation beyond the limits of plastic deformation, and (d) bowing or bend deformities within the limits of plastic deformation, but without fracture.

Epiphyseal fractures account for 10–20% of all fractures with peak incidence in adolescence. These fractures are more common in upper extremities, commonest being distal radius followed by distal tibia. Sudden traction of ligaments which attach over epiphysis and relative weakness of perichondrial ring are two important contributory factors for epiphyseal fractures.

According to *Salter and Harris classification*, epiphyseal fractures are classified into 5 types:

1. Simple epiphyseal separation from the physis,
2. Fracture involving physis and metaphysis,
3. Fracture involving physis and epiphysis,
4. Extended fracture involving physis, epiphysis and metaphysis and
5. Crush injury to physis

Management: Though detailed discussion of the fracture-treatment is beyond the scope of this book, some general principles are as follows:

- Most non-epiphyseal fractures heal excellently with simple immobilization for 2–3 weeks.
- Type I and II epiphyseal fractures need closed reduction but perfect alignment is unnecessary except in type II fracture of distal femur.
- Type III and IV fractures need perfect alignment with internal or external fixation.

Common indications for internal fixation are: (a) displaced epiphyseal or intra-articular fractures, (b) unstable fractures, (c) multiple or open fractures. External fixation is usually used for pelvic fractures or in cases with severe tissue/neurovascular injury.

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CHAPTER

24

Rheumatic Disorders

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Rheumatic disorders (*connective tissue disorders or collagen vascular disorders*) is a collective term to denote a large group of conditions with variable manifestations but two common characteristics: (a) acute or chronic inflammation of multiple target organs, specially musculoskeletal system and vasculitis, and (b) an underlying abnormal immune response, e.g. autoimmune etiology.

24.1 BASIC CONSIDERATIONS

Normally, immune system does not react to self-antigens due to elimination of autoreactive B- and T-cells during their development. This self-tolerance is lost in rheumatic disorders due to:

- *Cross-reactivity* between a foreign and self-antigen *due to* striking molecular similarity;
- *Alteration in host antigen* due to some extraneous factor, e.g. infection or drugs.

Genetic susceptibility as well as environmental factors have been identified to trigger these responses in rheumatic disorders.

Pathophysiologically, Non-recognition of self-antigen by own B and T-cells triggers an abnormal or exaggerated immune response against target tissues with—(a) recruitment of inflammatory cells, (b) immune complex formation, (c) complement activation, and (d) cytokine production; all leading to acute or chronic inflammation, tissue damage and constellation of clinical features.

Clinical spectrum of rheumatic disorders varies with the type, site and extent of immune injury. Possibility of rheumatic disease must be considered in presence of any one or more of the clinical indicators enumerated in **Table 24.1**, after exclusion of other common causes. Despite considerable overlap, rheumatic disorders may be broadly classified into three groups:

a. *Predominantly arthritic syndromes,* e.g. juvenile idiopathic arthritis (JIA).
b. *Systemic connective tissue disorders,* e.g. systemic lupus erythematosus (SLE), dermatomyositis, etc.
c. *Systemic vasculitis syndromes,* e.g. Henoch- Schönlein purpura (HSP), Kawasaki disease, etc.

TABLE 24.1: Clinical indicators of rheumatic disorders

- Unexplained prolonged fever
- Unexplained arthritis or arthralgia
- Unexplained muscular tenderness or weakness
- Enthesopathy, i.e. tenderness at ligamental insertions
- Recurrent or poly-serositis
- Unexplained skin rash or other acquired changes
- Unexplained multi-systemic disease

Laboratory diagnosis: No laboratory test is the gold standard in rheumatic disorders and diagnosis is usually based on constellation of *clinical features* (all of which may not be apparent at the time of first presentation, leading to delay in specific diagnosis) and *laboratory evidences* of chronic inflammation and immunological reactions. Important laboratory indicators of rheumatic disorders include:

a. ***Elevated acute phase reactants***, e.g. ESR, CRP, Ferritin, etc. due to chronic inflammatory process, which are also useful to monitor the course of illness and efficacy of therapy. However, these tests have limited diagnostic value, as also deranged in many non-rheumatic conditions, e.g. infections..
b. ***Rheumatoid factor (RF)*** is an IgM antibody directed against Fc segment of IgG antibodies, usually detected by latex-agglutination test. However, a positive rheumatoid factor is not necessarily diagnostic of rheumatoid disorders, being also positive in many viral infections, tuberculosis, infective endocarditis or intrauterine infections. Conversely, >85% cases with juvenile idiopathic arthritis are RF negative.
c. ***Antinuclear antibodies (ANA)*** are large group of auto-antibodies directed against antigens in the nucleus of the host cells, usually detected by indirect immunofluoroscence. ANA are present in 97% cases of SLE, but may also be positive in many other *rheumatological disorders,* e.g., Oligoarticular JIA or Juvenile dermatomyositis and *non-rheumatological conditions,* e.g., EBV, HIV, Tuberculosis and malignancies. ANA may be also present with low-titers

(1:40) in ~30% of normal individuals and with high titers (1:160) in ~5%.

Commonly used ANA test is a screening test, which detects presence of *non-specific* antinuclear antibodies. Tests to identify antibodies to specific extractable nuclear antigens (ENA) or ANA Blot/profile are also available, e.g., anti-Sm antibodies in SLE, anti- Scl antibodies in scleroderma and anti-Pm-Scl antibodies in dermatomyositis.

d. ***Lupus cell (LE cell)*** is a modified polymorph, ready-for-phagocytosis, after reacting with anti-nuclear antibody against its deoxyribonucleoprotein (DNP). While not very sensitive, presence of LE cells indicates possibility of rheumatological disorders.
e. ***MHC*** *(Major histocompatibility complex) or* ***HLA*** *(Human leukocyte antigen)* identification is mainly useful to predict the risk of rheumatic disorders in a suspected case or family members, e.g,. HLA-B27 for ankylosing spondylitis or HLA-DR4 for polyarticular rheumatoid arthritis.
f. ***Other immunological tests,*** though not diagnostic, help to assess the severity of disease and response to therapy and include, e.g. complement levels (C_3-C_4) or hypergammaglobulinemia, etc. which are more useful to assess the severity of disease and response to therapy.
g. ***Radiological investigations***, e.g., X-rays, USG, CT/MRI, help to establish the diagnosis and evaluate the extent of musculoskeletal involvement. USG is very useful to assess synovitis, joint effusions and enthesitis, as well as to guide joint aspirations and intra-articular drug injections.
h. ***Tissue biopsies*** are required to confirm the diagnosis in selected cases, e.g. skin biopsy in atypical Henoch-Schonlein purpura, muscle biopsy in uncertain cases of dermatomyositis and renal biopsy in suspected lupus nephritis. Synovial biopsy or joint fluid examination is rarely required in rheumatic disorders.

Management of rheumatological disorders requires multidisciplinary team approach including—(a) medical therapy with NSAIDs, steroids, *disease modifying anti-rheumatoid drugs* (DMARDs) and biological agents, (b) physiotherapy with orthopedic and orthotic interventions, (c) psychological counselling regarding chronic nature of these disorders, and (d) rehabilitation services.

DMARDs reduce inflammation by acting on inflammatory pathways and modulating the immune system, thus reducing the steroid requirements and include, e.g. methotrexate, cyclophosphamide, mycophenolate mofetil, sulfasalazine, etc.

Biological agents are target-specific monoclonal antibodies directed against various inflammatory agents, e.g. Rituximab (Anti-CD-20 antibody), Etanercept (TNF-α receptor antagonists), Anakinra (IL-1 receptor antagonists), etc.

24.2 JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA), previously known as *juvenile rheumatoid arthtritis*, is the leading cause of chronic arthropathy in children with intermittent exacerbations and residual deformities.

Rather than a single disease, JIA is a heterogeneous group of chronic arthritides and clear distinction between various subtypes is difficult. While there is no universal agreement on nomenclature and classification of JIA, one of the most acceptable one is the *International League of Associations for Rheumatology* (ILAR) classification **(Table 24.2)**.

Recently, *Pediatric Rheumatology International Trials Organizations* (PRINTO), 2019, has classified JIA in four homogenous clinical groups—(1) systemic JIA, (2) RF positive JIA, (3) enthesitis/spondylitis related JIA, and (4) early-onset ANA positive JIA.

Etiopathogenesis of JIA is complex and poorly understood, though definitely involves:

- An *autoimmune reaction* to external triggering factors, e.g. viral infections or joint trauma, and
- An *inherent susceptibility* to these reactions with specific HLA types – HLA-DR4 in polyarticular disease, and HLA-DR8/5 in pauciarticular disease. Non-HLA candidate loci are also associated with JIA, including polymorphisms in various genes encoding protein tyrosine phosphatise nonreceptor 22 (PTPN22), tumor necrosis factor (TNF)-α, macrophage inhibitory factor (MIF), interleukin (IL)-6, and IL-1 .

Eventually, abnormal immune response provokes chronic inflammation in target organs, responsible for tissue injury. T lymphocytes play a central role, releasing pro-inflammatory cytokines to favor Th-1 response. B cell activation, immune complex formation and complement activation also promote inflammation.

Pathologically, tissue injury is characterized by—(a) *hyperemia and edema* of sub-synovial tissues, (b) *pannus formation* over articular cartilage with destruction in late stages, and (c) *chronic inflammatory infiltration.*

Clinically, *Arthritis* is the hallmark of JIA, though the spectrum may vary from a solitary joint involvement

TABLE 24.2: ILAR classification* of JIA

- Systemic arthritis
- Polyarticular (Rheumatoid factor –ve)
- Polyarticular (Rheumatoid factor +ve)
- Oligoarthritis
- Enthesitis–related arthritis
- Psoriatic arthritis
- Undifferentiated arthritis

*abridged

to a systemic-onset disease where other systemic involvement precedes arthritis.

***Arthritis** in JIA*, irrespective of sub-types, is characterized by—(a) early morning stiffness, (b) joint swelling and restricted movements, disproportionate to local pain and other signs, (c) chronic course with intermittent exacerbations and residual deformity. Residual deformities are common after multiple attacks **(Fig. 24.1A)** and present as contractures, abnormal joint shapes, asymmetric limb length with postural abnormalities, e.g. scoliosis, and undergrowth of affected joints, e.g. micrognathia due to temporomandibular joint involvement.

Extra-articular manifestations are more common in systemic-onset or polyarticular disease and include: (a) anterior uveitis, with red-eye, posterior synechiae, glaucoma and blindness in untreated cases, (b) serositis, e.g. pericardial/pleural effusion, (c) chronic renal disease, and (d) rare cardiovascular, pulmonary or neurological complications.

Of various sub-types of JIA discussed below **(Table 24.3)**, All are 3-10 times more common in females, except systemic JIA with equal sex ratio. Cases with oligoarthritis have earlier onset (3–4 years) than others.

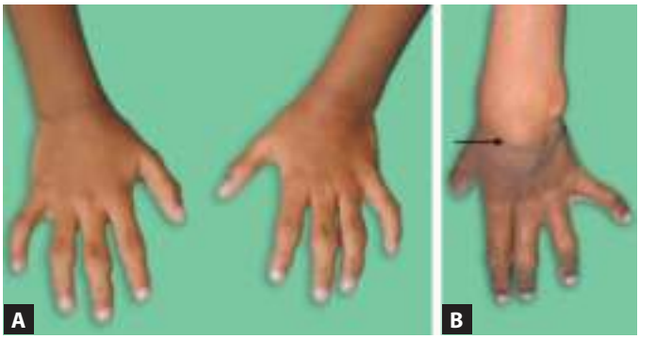

Fig. 24.1A and B: Juvenile idiopathic arthritis: (A) Finger deformities; (B) Rheumatoid nodule

- **Oligoarticular** *JIA* is the commonest and mildest subtype (40–50%). Clinically, it affects four or less joints during first 6 months of disease, as asymmetrical involvement of large joints of legs, e.g. knees and ankles. Small joints are usually spared. Isolated involvement of upper limb joints and hip is rare. Swelling is more prominent than pain.

  Two clinical variants of oligoarthritis include - *Persistent oligoarticular JIA* limited to four or less joints even after 6 months; and *Extended oligoarticular JIA* with involvement of >4 joints after 6 months period with poorer prognosis.

  Extra-articular manifestations are rare except asymptomatic or symptomatic uveitis in ~25%, more common in ANA-positive girls.
- **Polyarticular JIA** occurs in 25–30% cases, characterized by inflammation of 5 or more joints within 6 months of the onset of disease. Unlike oligoarthritis, Pain is more prominent than swelling. Clinical course differs in RF-ve and RF+ve cases of polyarticular disease.

  RF–ve cases are less severe and usually involve larger joints of knee, wrist, ankle and hips. Small joints are less commonly affected and Rheumatoid nodules are not seen.

  RF+ve cases have more aggressive disease resembling symmetric arthropathy of adult rheumatoid arthritis, typically involving small joints, cervical spine and temporomandibular joint.

  Rheumatoid nodules are seen almost exclusively in RF-positive individuals over extensor surfaces of the elbows, spine and scalp and indicate more severe course **(Fig. 24.1B)**. These nodules arise from synovial sheaths and tend to be better palpable than visible (*d/d rheumatic nodules*, which are subcutaneous and better visible than palpable).

TABLE 24.3: Important differences between various sub-types of JIA

	Oligoarthritis	***Polyarticular***		***Systemic***
	Type I	***Rh-ve***	***Rh+ve***	
Frequency	40–50%	20–35%	10%	5–15%
Age of onset	< 5 years	< 5 or > 10 years	> 10 years	< 5 years
Sex (F:M)	F (3:1)	F (3–10:1)	F (4:1)	Equal (1:1)
No. of joints	< 5	> 5	> 5	Late, < 5
Type of joints	Large	Small/large	Small/large	Large/small
Hip arthritis	No	No	Common	No
Enthesitis	No	Rare	Nodules	±
Systemic signs	Uveitis (< 25%)	Rare	Uncommon	Rash, others
Rh factor	Very rare	–ve	Positive	–ve
ANA	>50%	40%	50%	–ve
HLA	DR 8/5, B27	–	DW4/DR4	–
Prognosis	Good	Good	Poor	Worst

- **Systemic-onset JIA** is the most severe sub-type, which presents with: (a) quotidian *fever* with daily spikes, more in evenings, for >2 weeks, (b) typical macular *rash* over trunk and proximal extremities that comes and goes with fever spikes, (c) arthritis, usually polyarticular, after 2–6 months of systemic features (though arthralgia and myalgia may be present on onset), and (d) early extra-articular manifestations, e.g. hepatosplenomegaly, lymphadenopathy and serositis.

  Macrophage activation syndrome (MAS) is a rare but potentially fatal complication of systemic-onset JIA, which can develop any time during the course of disease. MAS presents with acute spiking fevers, lymphadenopathy, hepatosplenomegaly, and encephalopathy. ESR falls and helps to differentiate MAS from acute flare of systemic JIA. Thrombocytopenia with high ferritin levels is common and bone marrow shows macrophage hemophagocytosis.

  Diagnosis of MAS rests on a combination of clinical and laboratory criteria, in a febrile child with known or suspected JIA as follows—(a) serum ferritin >684 ng/ml, and (b) any *two or more* of the following – platelet cunt <181/10^9/L, Aspartate Aminotransferase (AST) >48 U/L, Triglycerides >156 mg/dl or fibrinogen 360 mg/dl. *(PRINTO criteria 2016)*.

  Emergency treatment includes high-dose steroids (IV Methylprednisolone) or IVIG, while other options include cyclosporine and biological agents, e.g. Anakinra in severe cases.
- **Psoriatic arthritis** is an asymmetrical oligoarthritis of large or small joints, associated with—(a) psoriasis, *or* (b) any two of the following features – dactylitis, nail pitting (onycholysis) or history of psoriasis in a first-degree relative. ANA is frequently positive and spinal involvement is seen only in cases with HLA-B27 association. Arthritis may precede, accompany or succeed psoriasis.
- **Enthesitis-related arthritis** is more common in older boys (9–10 years) with asymmetrical involvement of the large joints of lower limbs and *Enthesitis*, i.e. inflammation at the site of attachment of ligaments, presenting as localized tenderness around the foot and knee. Many of these cases are HLA-B27 positive and develop ankylosing spondylitis after adolescence. Acute self-limiting iritis may develop in 25% but chronic iridocyclitis is rare.
- **Undifferentiated JIA** refers to those cases which fit no other category or fit more than one category.

Diagnosis of JIA is mainly clinical, as no laboratory investigation is pathognomonic.

Clinical diagnosis as well as sub-typing of JIA is based on a clinical criteria **(Table 24.4)** and may not always be accurate in early stages due to gradual evolution of signs, e.g. polyarticular change from early pauciarticular disease *or* absence of joint involvement in early systemic disease. *It is prudent to wait for ~6 months before final sub-typing the JIA.*

TABLE 24.4: ILAR diagnostic criteria for JIA

Age of onset <16 years,
Arthritis for >6 weeks, with
- Joint swelling/effusion or
- Any two of the following:
  - Restricted active movements
  - Painful/tender movements
  - Increased joint temperature (hot joints)

Pattern of joint involvement
- Oligoarthritis* (Persistent or extended)
- RF-negative polyarthritis
- RF positive polyarthritis
- Systemic arthritis
- Psoriatic arthritis
- Enthesitis-related
- Undifferentiated

Exclusion of other causes of arthritis

*Oligoarthritis is further classified as:
- *Persistent:* ≤ 4 joints are involved throughout course of disease
- *Extended:* > 4 joints are involved after first 6 months

Laboratory diagnosis is largely supportive and includes:
- *Indicators of chronic inflammation*, i.e. elevated ESR, CRP, leukocytosis help in monitoring the activity of disease. Serum ferritin is elevated though markedly high values suggests possibility of MAS.
- *Indicators of immunological reactions*, e.g. ANA and Rh factor have diagnostic as well as prognostic value. ANA is positive in >50–70% cases, except systemic-onset disease. RF is positive in only <10% cases, usually with polyarticular disease and poor functional prognosis.
- *Radiological abnormalities* in involved joints appear only after few weeks and include—(a) soft tissue swelling and increased joint space due to effusion and osteopenia in early stages, followed by (b) subchondral erosion on articular surface (*pannus* formation) with decreased joint space, and (c) bony destruction or ankylosis in later stages.
- *USG or MRI* of involved joints is useful for early diagnosis of JIA before appearance of X-ray abnormalities and detect minor inflammatory changes, e.g. synovial thickening, joint effusion, etc.
- *Synovial fluid aspiration* for microscopy and culture is indicated in cases with monoarthritis to exclude other causes, e.g. septic or tubercular arthritis.

D/D of JIA depends on the clinical sub-types and includes various causes of chronic arthritis **(Table 24.5)**.
- *D/D of Polyarticular JIA* includes rheumatic fever **(Table 24.6)**, SLE (butterfly rash), vasculitis syndromes, e.g. Kawasaki disease or Henoch-Schönlein purpura (typical rash) and leukemia.

TABLE 24.5: Causes of chronic arthritis in children

- **Juvenile idiopathic arthritis**
- **Spondyloarthropathies**
  - Juvenile ankylosing spondylitis
  - Psoriatic arthritis
  - Chronic reactive arthritis
  - Arthritis with inflammatory bowel disease
- **Connective tissue disorders**
  - Systemic lupus erythematosus
  - Juvenile dermatomyositis
  - Scleroderma
- **Vascular:** Legg-Calve-Perthes disease
- **Infections:** Tubercular arthritis
- **Hematologic:** Hemophilia
- **Metabolic:** Gout, sarcoidosis
- **Others:** Post-traumatic degeneration

TABLE 24.6: D/D juvenile idiopathic arthritis vs rheumatic arthritis

	JIA	***Rheumatic A.***
Epidemiology		
Age	>2–16 years	5–10 years
Sex	F > M	M > F
History of sore throat	Absent	Present
Arthritis		
Type	Small joints	Large joints
Duration	Chronic	Acute
Progression	Polyarticular	Migratory
Axial joints	Yes	Spared
Morning stiffness	Yes	No
Extra-articular		
Enthesitis	Common	No
Skin nodules	Deep, palpable	S/C, visible
Cardiac signs	Rare	Common
Investigations		
ASO	Negative	Positive
ANA	+ve in >50%	Negative
Rheumatoid F	+ve in <10%	Negative
Joint prognosis	Residual ++	No residue

- *D/D of Oligoarticular JIA* includes other causes of acute joint pain, e.g. septic arthritis, tubercular arthritis, joint trauma and Lyme disease.

  Lyme disease, rare in India, is a vector-borne disease due to spirochete – *Borrelia burgdorferi*, with typical skin lesion (*erythema chronicum migrans)* and recurrent large-joint arthritis.
- *D/D of systemic JIA* includes reactive arthritis, vasculitis syndromes, e.g. Kawasaki disease and leukemia.

Management of JIA aims for—(a) control of acute joint and systemic symptoms, (b) prevention of exacerbations and long-term deformities, and (c) physical rehabilitation.

a. **Anti-inflammatory therapy** is the cornerstone of management, though the choice of drugs depends on severity of disease and response to therapy.

- ***Non-steroidal anti-inflammatory drugs,*** e.g. Naproxen (PO 10–20 mg/kg/day q12hr), Ibuprofen (30–40 mg/kg/day q8hr) or Diclofenac (2–3 mg/kg/day q8hr) are first-line agents in acute phase of JIA, though clinical response may vary and treatment should continue for at least 6 weeks before changing the drug. Despite symptomatic relief, these agents do not affect progression of disease. Aspirin is no longer used due to potential risk of Reye syndrome, while safety of selective COX-2 inhibitors, e.g. rofecoxib, is not established in children.
- ***Disease modifying anti-rheumatoid drugs*** *(DMARDs)*, e.g. Methotrexate is the safest and most-effective drug for long-term treatment of JIA, given as PO/SC 15–20 mg/m^2 weekly (max 25 mg/m^2 week), till remission is achieved, followed by gradual tapering to the minimum effective dose for at least 1–2 years.

  Adverse effects are rare, though periodic liver function tests and complete blood counts are advised due to potential risk of hepatic fibrosis and marrow suppression on prolonged use.

  Other DMARDs in use include sulfasalazine, Leflunomide, etc. Old-generation drugs, e.g., penicillamine and gold salts are no longer used at present routinely due to adverse effects.
- ***Biological agents,*** which inhibit pro-inflammatory cytokines, e.g. TNF-α, IL-1, and IL-6 are used as second-line drugs in cases with poor response to DMARDs. TNF-α antagonists (e.g., *etanercept*, *adalimumab*) are preferred over other agents except systemic JIA, in whom systemic steroids followed by the IL-1 or IL-6 antagonist therapy (with *Canakinmab* or *Tocilizumab* respectively), often induces more rapid response.
- ***Steroids:*** With advent of newer DMARDs, the systemic steroids are recommended only for severe systemic illness, *or* as bridge therapy till the response to DMARDs, *or* for control of uveitis. Topical steroids are also used as intra-articular injections in non-responding pauciarticular lesions.
- ***Other Interventions,*** e.g., plasmapheresis, gene therapy, and stem-cell transplant have been approved in adults with severe refractory cases, but not yet in children.

b. **Supportive therapy** in JIA includes—(a) occupational and physical therapy, (b) nutritional support, specially to ensure adequate iron and calcium intake, (c) psychosocial support, (d) surgical/orthopaedic correction of deformities, and (e) regular follow-up, specially with periodic slit-lamp examination to exclude asymptomatic uveitis.

Outcome of JIA depends on clinical type with best prognosis in persistent oligoarticular JIA and worst in systemic JIA or RF+ve polyarticular disease. About half

of JIA cases enter adulthood with active disease and functional limitations of variable severity, though outlook has improved with recent advances in management.

Late complications of JIA include—(a) joint contractures and deformities, (b) growth abnormalities with limb-length discrepancies, and (c) very rarely, amyloidosis.

24.3 SYSTEMIC CONNECTIVE TISSUE DISORDERS

Although the term *connective tissue disorders or collagen disorders* is also applicable to other rheumatic and non-rheumatic disorders, e.g. Ehlers-Danlos syndrome, this chapter deals with those conditions, which generally present as multi-systemic inflammatory disorders.

24.3.1 SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disorder, characterized by presence of antinuclear antibodies (ANA) and inflammatory damage to virtually any organ, especially skin, synovium, blood cells, kidney and CNS.

Epidemiology: SLE is one of the commonest rheumatological disorders, predominantly affecting females (> 4:1) with peak age of onset in adolescence, frequently corresponding to menarche.

Etiopathogenesis involves *hallmark* development of autoantibodies against many cell antigens, e.g. DNA, other nuclear antigens and blood cells, leading to immunecomplex mediated injury in target organs.

While exact cause for autoimmune phenomena is obscure, important hypotheses suggest—(a) *genetic basis* with high incidence of disease in certain HLA types, e.g. B8, DR2 and 3, (b) *defective apoptosis* of self-reactive T-cells in fetal life, (c) *non-specific response to a specific antigen*, e.g. virus or drugs, and (d) *role of female sex hormones* in altered immune response.

Pathology in target organs is characterized by presence of fibrinoid deposits in vascular walls and certain hematoxylin stained bodies (LE cells) in parenchymal tissues. *LE cell* is a modified polymorph, ready for phagocytosis after reacting to antinuclear antibody against own deoxyribonucleoprotein (DNP).

Clinical presentation: SLE is rare below 5 years of age, usually diagnosed in adolescent females. Natural course is highly unpredictable, ranging from chronic smoldering disease to acute life-threatening illness. Most cases begin with:

a. *Constitutional symptoms*, e.g. prolonged fever, weight loss and fatigue.
b. *Butterfly skin rash* over malar prominences and nasal bridge **(Fig. 24.2)**, which may be photosensitive and varies in appearance from a simple erythematous flush to thickened epidermis with scaly patches. Other skin lesions, e.g. discoid lesions, vasculitis purpura or *livedo reticularis* (generalized lace-like discoloration) are common but not diagnostic.
c. *Arthralgia or arthritis,* specially involving small joints and disproportionately more painful than local signs. Residual deformities are uncommon during childhood.
d. *Renal involvement* of variable severity (*Lupus nephritis*) in 30–40%, presenting with hematuria, proteinuria, hypertension and renal failure. Lupus nephritis is pathologically classified into six types (I-VI) and renal biopsy is essential for therapeutic decision making.

Fig. 24.2: Systemic lupus erythematosus: Butterfly rash.

Other important systemic manifestations of SLE may appear during the course of disease and include:

- *GIT* involvement as abdominal pain, diarrhea, melena, etc. due to peritoneal serositis and/or vasculitis,
- *Pulmonary* involvement as pleuritis or hemorrhage,
- *Neurological* involvement as seizures, psychosis or strokes,
- *Cardiac* involvement as pericarditis, conduction defects, coronary vasculitis, CCF, and
- *Hematological* involvement with Coombs-positive hemolytic anemia, thrombocytopenia, etc.

Diagnosis rests on the essential presence of *Entry crite*ria, i.e. ANA Positivity >1:80 on Hep2 cells or equivalent test, *and* a total score of 10 (including 1 clinical criteria) on additive criteria, as per EULAR/ACR classification Criteria 2019 **(Table 24.7)**. Additive criteria may be present at the same or different times during course of illness and must have no alternative explanation.

Important laboratory investigations include:

- *Screening ANA test*, to detect non-specific antinuclear antibodies, which are present in almost all cases of SLE

TABLE 24.7: EULAR/ACR* criteria for diagnosis of SLE

Entry criteria (Essential) ***ANA positive >1:80 on Hep2 cells or equivalent positive test***

Additive criteria ***(+Total score of ≥10 and ≥1 clinical criteria)***

Clinical domain and criteria	*Score*	*Immunological Domain and Criteria*	*Score*
Fever	4	**Antiphospholipid antibodies** (any) Anticardiolipin Anti-β_2 glycoprotein-1 Lupus anticoagulant	2
Hematological		**Complement proteins**	
Leukopenia	3	Low C_3 *or* C_4	3
Thrombocytopenia	4	Low C_3 *and* C_4	4
Autoimmune hemolysis	4		
Neuropsychiatric		**SLE-Specific antibodies**	6
Delirium	2	Anti-dsDNA, or	
Psychosis	3	Anti-Smith antibody	
Seizures	5		
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous/ discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Renal			
Proteinuria >0.5 gm/24 hrs	4		
Biopsy: Lupus nephritis II/V	8		
Biopsy Lupus nephritis III/IV	10		

*European League Against Rheumatism/American College of Rheumatology

- *Do not count a criteria in presence of alternative explanation*
- *Presence of criteria at least on one occasion is sufficient*
- *Criteria need not be present simultaneously*
- *Within each domain, only highest weighted criterion must be counted*

but also in other rheumatic and infective conditions (Ch 24.1). A false-positive VDRL test or RF may also suggest SLE in suspected case.

- *Anti-ds DNA* test to detect lupus-specific anti-DNA antibodies, which also reflect degree of disease activity. *Anti-Sm antibodies* are also lupus-specific.
- *Low serum complement levels* (CH_{50}, C_3, C_4), which gradually normalize with remission, are useful to monitor response to therapy.
- *Tests for other tissue-specific antibodies*, e.g. Coombs test, anti-thyroid antibodies, etc. in selected cases.
- *Organ-specific Investigations*, e.g. renal biopsy or radioimaging with USG/CT/MRI in selected cases.

Management depends on the extent and severity of disease, guided by clinical features and serological markers (Anti-ds DNA antibodies, complement levels):

- ***Mild and localized disease,*** without renal or life-threatening organ involvement is generally treated with NSAIDs and hydroxychloroquine (PO 3–5 mg/kg/day). Retinal toxicity is a major concern on hydroxychloroquine therapy and needs regular ophthalmic monitoring.
- ***Moderate multisystemic disease,*** but without life-threatening involvement of kidneys or other vital organs, is treated with corticosteroids, i.e. Prednisolone (PO 1–2 mg/kg/day) in divided doses till normalization of complement levels, followed by single dose alternate-day therapy for next 2–3 years. Severe cases may be treated with IV pulse methylprednisolone (30 mg/kg OD for 3 days) initially, followed by oral steroid therapy. Steroid-sparing agents, e.g. hydroxychloroquine, mycophenolate or azathioprine may be used with steroids for long-term treatment.
- **Severe multisystemic disease and presence of Class III or IV lupus nephritis** requires aggressive therapy with drugs, e.g. cyclophosphamide and biologic agents, e.g. Rituximab.

Role of other modalities, e.g. cyclosporine, hormone therapy, stem-cell transplant and anti-cytokines is in experimental stage.

Additional therapy is indicated in selected cases, e.g. anticoagulant therapy in thrombotic episodes, antihypertensives in renal disease, anticonvulsants in CNS disease, etc.

Avoidance of direct sun exposure and use of sunscreens in advised to all cases, apart from other supportive measures.

Prognosis: 5-year survival rate is ~85% with current therapeutic regimes, though some patients may ultimately succumb to renal disease, cerebrovascular events or therapy-related opportunistic infections.

Neonatal lupus: Newborns born to mothers suffering from SLE may develop neonatal lupus due to transplacental transfer of antibodies (specially anti-RO/SSA and anti-LA/SSB antigens), presenting with-(a) congenital heart block, (b) cutaneous lesions, (c) hematological manifestations, e.g. hemolytic anemia or thrombocytopenia, and (d) rarely, other systemic manifestations. All newborns with antibody transfer do not necessarily manifest clinically and most manifestations resolve soon after birth. However, congenital heart block is permanent and requires cardiac pacing.

Drug-induced lupus: Many drugs have been implicated in presentation of lupus-like features or aggravation of SLE, including anticonvulsants, e.g. Phenytoin, Carbamazepine, Valproate etc. Antitubercular drugs, e.g. INH and Rifampicin and others, e.g. penicillamine, Amiodarone, and Procainamide, etc.

24.3.2 JUVENILE DERMATOMYOSITIS

Juvenile dermatomyositis (JDM) is the commonest inflammatory myopathy in childhood, characterized by typical rash and symmetrical proximal myopathy.

Etiology is idiopathic, probably an autoimmune disorder with inherent genetic susceptibility, triggered by preceding intestinal or respiratory infections. JDM is more common with certain HLA types (B8, DQA1) and following group A streptococci, coxsackievirus B or parvoviral infections.

Pathologically, it is characterized by an underlying vasculopathy with immune complex and complement deposition, leading to vascular occlusions and infarcts, inflammatory cell infiltration and extensive fibrosis in skin and muscles.

Clinically, it is more common in females with peak age of onset between 8 and 12 years, which is usually insidious with vague constitutional complaints, followed by:

- *Characteristic violaceous rash* over upper eyelids (*Heliotrope eyelids*), with or without periorbital puffiness and telangiectasia. Other skin lesions include similar rash on other sun-exposed parts and hypertrophic pale red papules over metacarpal or proximal interphalangeal joints, i.e. *Gottron papules* **(Fig. 24.3)**.
- *Slowly progressive symmetrical muscular weakness* after 2–3 months of rash, presenting with functional impairment, e.g. difficulty to climb stairs, sit or stand from supine position (positive Gower sign), raise the head, etc. Affected muscles may be tender in acute phase. Gradually, severe manifestations appear, e.g., dysphagia, nasal regurgitation or respiratory paralysis. Smooth muscles involvement may lead to constipation and dilated cardiomyopathy.
- *Complications* may result due to muscular weakness or diffuse vasculopathy and include—(a) recurrent aspiration, interstitial pneumonia or fibrosing alveolitis, (b) intestinal perforation or bleeding, (c) seizures, (d) retinitis, (e) mucosal ulcerations, and (f) calcinosis, i.e. calcium deposits in muscles and subcutaneous tissues in late stages.

Fig. 24.3A and B: Juvenile dermatomyositis: (A) Heliotrope eyelids; (B) Gottron papules.
(*Courtesy:* Dr Raju Khubchandani)

TABLE 24.8: Diagnostic criteria for dermatomyositis

- Typical rash (Heliotrope eyelids, Gottron papules) and
- Any *three* of following features
  - Symmetrical proximal muscle weakness
  - Elevated muscle enzymes (CPK, LDH)
  - Typical EMG findings*
  - Muscle biopsy suggestive of chronic inflammation

*Fasciculations, irritability and high-frequency discharges

Diagnosis depends on essential presence of typical rash with any three of the clinical or laboratory evidence of muscular injury **(Table 24.8)**. Presence of only two of these evidences (instead of 3) with rash is considered as a probable case.

MRI helps to identify exact site of active disease for biopsy and EMG studies, as well as to make an early diagnosis before appearance of muscle enzyme abnormalities. ESR is usually normal and ANA is present in >80% cases. Soft-tissue calcinosis may be seen on X-rays and pulmonary function tests may reveal restrictive lung disease.

D/D includes other rheumatoid disorders with rash, e.g. SLE or other causes of myopathy, e.g., vial myositis, metabolic myopathies, etc.

Treatment revolves around *steroid therapy* (PO prednisolone 2 mg/kg/day) till normalization of muscle enzymes and clinical recovery, followed by low-dose alternate-day therapy for minimum 2 years. In severe cases,

IV methylprednisolone may be used in initial stages, followed by oral prednisolone maintenance. PO/IV/SC Methotrexate (15 mg/m^2/day) may be used as steroid-sparing agent along with folic acid supplements.

Hydroxychloroquine (PO 3–5 mg/kg/day) is used as a second-line disease modifying agent. In steroid-resistant/dependent cases, other drugs, e.g. cyclophosphamide, cyclosporine, rituximab or IV immunoglobulins may be considered.

Supportive therapy includes use of sunscreens to prevent rashes, nasogastric feeding in dysphagia, and ventilatory support for respiratory paralysis. Physical and occupational therapy with muscle stretching exercises should begin as soon as acute inflammation subsides.

Prognosis has markedly improved with aggressive immunosuppressive therapy, though acute phase may last for 12–18 months and recovery is better in children than in adults. Overall mortality is <5%, though long-term disabilities are common even in treated cases.

24.3.3 SCLERODERMA

Scleroderma is an autoimmune disorder of predominantly adults, characterized by *hardening of—(a) skin* due to chronic fibrosis of dermis and deeper tissues, *and/or (b)* arteries of internal organs specially lungs, kidney and GIT with *systemic manifestations*. It is very rare in children and usually presents with localized rather than systemic disease.

Etiopathogenesis is autoimmune, suggested by—(a) histological features, i.e. destruction of vascular endothelium, cellular infiltration, fibroblast proliferation and increased collagen synthesis, and (b) presence of antinuclear antibodies in some cases. Rarely, drugs, e.g. bleomycin or chemicals, e.g. PVC exposure has been implicated as triggering event.

Clinically, *Raynoud phenomena*, i.e. transient episodes of pallor followed by cyanosis and then followed by erythema (3-stages), over fingers and toes after cold exposure due to arterial spasm in digits, is the earliest manifestation preceding skin and visceral manifestations.

Localized scleroderma is more common in children, presenting with discrete lesions (*morphea*) on trunk *or* linear lesions on extremities, which begin as an inflammatory patch but rapidly evolve to indurated, depigmented and atrophic lesions with tightening of skin. Fibrosis sometimes extends to deeper tissues, e.g. muscles and bones, leading to contractures, limb-shortening and cosmetic deformities.

Systemic sclerosis is extremely rare in childhood, presenting with (a) *progressive dermal involvement*, with flexion contractures, and (b) *multi-systemic involvement, e.g.* progressive pulmonary interstitial fibrosis, hypertension, dysphagia and CCF or arrhythmias due to cardiac fibrosis.

TABLE 24.9: Diagnostic criteria for Juvenile systemic sclerosis

- **Major criteria (required)**
  - Proximal skin sclerosis or induration
- **Minor criteria (at least 2)**
  - Sclerodactyly
  - Peripehral vasculopathy*
  - Dysphagia, gastroesophageal reflux
  - Cardiac arrhythmia, CCF
  - Renal crisis, hypertension
  - Pulmonary fibrosis/hypertension
  - Neuropathy, carpal-tunnel syndrome
  - Tendon friction rubs, arthritis, myositis
  - *Serology:* Positive for antinuclear antibodies**

* Raynaud phenomenon, nail-fold telangiectasias, digital tip ulcers
** SSc-selective autoantibodies (anticentromere, antitopoisomerase I [Scl-70], antifibrillarin, anti-PM/Scl, antifibrillin or anti-RNA polymerase I or III)
Abridged from ES/ACR/EULAR criteria 2007

Diagnosis is clinical, supported by *nail-fold capillaroscopy* to reveal vascular changes (loss, tortuosity, bushy capillaries) and presence of antinuclear antibodies **(Table 24.9)**.

Serial pulmonary function tests for vital capacity and CO-diffusion capacity are indicated to assess lung functions. .

Treatment depends on the severity of disease and includes:

- Immunosuppressive therapy with steroids (PO Prednisolone 2 mg/kg/day) or SC Methotrexate (15 mg/m^2/week) or both, for 4–6 months. Mycophenolate is the second-line drug for recalcitrant disease.
- Physical and occupation therapy for contractures.
- Avoidance of cold-exposure (gloves) and drugs, e.g. nifedipine or topical vasodilators to prevent Raynaud phenomenon.

Prognosis is variable, with regression or stabilization of localized lesions after many years, or progression to systemic sclerosis with death due to end-stage pulmonary, renal or cardiac disease.

Other rare but important connective tissue disorders in children include:

Sjogren syndrome is a chronic inflammatory disease of autoimmune origin, clinically characterized by: (a) dry eyes, e.g. keratoconjunctivitis sicca *or* xerophthalmia, (b) dry mouth, i.e. xerostomia, and (c) systemic manifestations of connective tissue disease involving skin, muscles and joints, serosal cavities and CNS or other organs. It is typically seen in females (9:1) of 35–45 years age, rare in children.

Behçet's disease is a rare multi-systemic disorder in childhood, characterized by recurrent oral and genital ulcerations with/without other manifestations of connective tissue involvement.

Mixed connective tissue disease (MCTD) is a multisystemic disorder, characterized by overlapping features of JRA, SLE, systemic scleroderma and dermatomyositis. These patients characteristically have high titers of U1-anti-ribonucleoprotein (anti-RNP) antibodies, along with anti-DNA antibodies. Treatment includes low-dose steroids/NSAIDs and long-term weekly methotrexate therapy.

24.4 VASCULITIS SYNDROMES

Vasculitis syndromes include a spectrum of systemic disorders with common pathology-*idiopathic or immune-complex mediated damage to vascular endothelium.* Depending on the size of predominantly involved vessels, these syndromes may be broadly classified as:

- *Large vessel* vasculitides, e.g. Takayasu disease,
- *Medium vessel* vasculitides, e.g. Kawasaki disease or polyarteritis nodosa, and
- *Small vessel* vasculitides, e.g. Henoch-Schönlein purpura, Wegener's granulomatosis, etc.

24.4.1 HENOCH-SCHÖNLEIN PURPURA (IgA VASCULITIS)

Henoch-Schönlein purpura (HSP) or *Anaphylactoid purpura* is the commonest vasculitis syndrome as well as the commonest cause of non-thrombocytopenic purpura in children.

Etiopathogenesis: HSP is an acute IgA-mediated vasculitis of *small vessels*, with presence of IgA and C_3 deposits in skin, GIT and renal vasculature. Tissue damage is probably caused by release of cytokines, e.g. TNF- and IL-6, following immune activation. Most cases are preceded by viral or streptococcal upper respiratory infections and some HLA types (B34, DRB1*01) have been linked to the increased risk of disease.

Clinically, HSP is most common between 2–8 years of age, in males (2:1) and during winter months. Onset may be acute or insidious, with/without preceding prodromal non-specific illness.

Skin lesions are hallmark of HSP, beginning as pinkish macules and papules, which rapidly evolve to *palpable purpura, with typical distribution* in dependent parts, i.e. legs and buttocks below the waist or loose connective tissues, e.g. eyelids, scrotum and dorsum of foot and hands **(Fig. 24.4)**. These lesions, which are typically palpable, tend to appear in crops for 1–2 weeks and fade after 1–2 weeks with gradual color change from red > purple > brown. Edema of the affected parts may precede or co-exist with purpuric lesions.

Other manifestations include: (a) GIT involvement (50–70%) with crampy abdominal pain or bleeding due to mesenteric vasculitis, (b) joint involvement (~80%) with arthritis of knee/ankles due to synovial effusion but without articular damage, (c) renal involvement (20–80% cases) with hematuria, or proteinuria due to glomerular injury; and rarely, (d) others, e.g. encephalopathy, pulmonary hemorrhage, etc.

Fig. 24.4: Henoch-Schönlein purpura.

TABLE 24.10: Diagnostic criteria for Henoch-Schönein purpura

- Palpable Purpura ***with***
- Any one of the following:
  - Abdominal pain (acute, diffuse, colicky)
  - Arthritis or arthralgia
  - Tissue biopsy s/o predominant IgA deposits
  - Renal involvement (proteinuria/hematuria/RBC casts)

*Abridged from EULAR/PRINTO/PRES criteria 2010

Most cases recover spontaneously within 2–3 weeks, but ~10% may relapse intermittently for 1–2 years.

Diagnosis is largely clinical, based on the presence of palpable purpura without coagulopathy or thrombocytopenia, *and* at least one of the systemic features *or* predominant IgA deposits on biopsy, as per EULAR/PRINTO/PRES criteria 2010 **(Table 24.10)**.

Skin biopsy reveals leukocytoclastic vascultitis with granulocytes in the walls of arterioles or venules, though not necessary in all cases and recommended only in atypical ones to exclude other causes of vasculitis, e.g. ANCA-associated vasculitis.

Other laboratory abnormalities include anemia, leukocytosis, raised ESR and hypergammaglobulinemia. ANA and RF are negative. Serial urine examination is indicated during acute phase for early detection of renal involvement.

Treatment is supportive, including: (a) bed rest to avoid further edema or purpuric lesions, (b) mild analgesics, e.g. paracetamol for pain control, and (c) monitoring and treatment for renal or GIT complications.

Steroids are not indicated, except in cases with acute GIT or CNS complications or persistent renal

damage. IV Immunoglobulins, plasmapheresis and immunosuppressive therapy have been used in severe and/or chronic cases.

Outcome: Nephritis is an important complication in 1–2% and all recovered patient should be periodically followed-up for renal disease for several months. Risk of recurrence of HSP is 15–60%.

24.4.2 WEGENER GRANULOMATOSIS

Wegener granulomatosis (*Granulomatosis with polyangiitis* or GPA) is a rare small-vessel vasculitis in children, affecting respiratory and renal vasculature, with characteristic necrotizing granuloma formation.

Clinically, most cases present in or beyond adolescence, as chronic sinusitis, chronic pulmonary disease with hemoptysis or as glomerulonephritis.

Diagnosis rests on chest X-ray/CT-scan to reveal nodular opacities and necrotising granulomatous angiitis on renal/lung/sinus biopsy. ANCA (antineutrophilic cytoplasmic antibodies) are positive in >90% cases and the presence of anti-PR3 is specific.

Treatment includes immunosuppressive therapy with steroids, cyclophosphamide or methotrexate, though.

Complications due to enlarging granulomas, e.g. orbital or ear involvement, pulmonary hemorrhage and chronic renal failure are common.

24.4.3 KAWASAKI DISEASE

Kawasaki disease (KD), is an emerging common cause of acquired heart disease in children after control of rheumatic fever. First described in Japan (Dr Kawasaki, 1967), it is not uncommon in other parts of world including India, though many cases remain undetected.

Etiopathogenesis: KD is a *multi-systemic vasculitis of predominantly medium-sized vessels*, with special predilection to coronary arteries.

Acute phase is characterized by intense vascular inflammation involving all three layers and destruction of internal elastic lamina. Gradually, vessel wall weakens and loses its elasticity, leading to aneurysmal dilatation, stasis, thrombosis and obstructed blood flow. In recovery phase, lesions become fibrotic with subsequent stenotic occlusion.

While exact etiology is not established, available evidences suggest an infective origin with genetic predisposition, based on following facts—(a) periodic epidemics, (b) self-limiting nature, (c) clinical picture of fever, rash and lymphadenopathy, and (d) rarity of disease in first 3 months of life (? due to maternal antibodies) or adults (? due to acquired immunity). Recent outbreak of Kawasaki disease during COVID-19 pandemic reiterates role of viral triggers in genetically susceptible individuals.

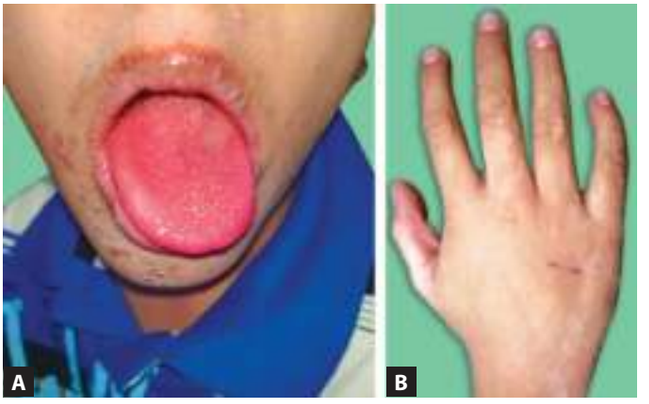

Fig. 24.5A and B: Kawasaki disease: (A) Strawberry tongue; (B) Periungual peeling of skin.

Role of genetics in causation of KD is suggested by higher incidence of disease in asian children and in those with similar family history. Significant association of KD with polymorphisms in the *ITPKC* gene - a T-cell regulator, is known.

Clinically, Over 80% of cases are seen <5 years of age, with male preponderance. Presentation evolves over a period of time with three distinct phases:

- ***Acute febrile phase*** (0–2 weeks) with - (a) high fever, (b) mucosal changes, e.g. conjunctivitis, oropharyngeal erythema with *strawberry tongue* and cracked lips, (c) cervical lymphadenopathy, (d) polymorphic truncal rash and (e) skin changes over peripheral extremities with erythema and/or induration of palms and soles **(Fig. 24.5)**. Child tends to be extremely irritable during this phase and some may also have arthritis, aseptic meningitis or diarrhea. Macrophage activation syndrome may develop in some cases of KD during acute phase.
- ***Sub-acute phase*** (2–4 weeks) with—(a) gradual disappearance of fever and other symptoms, (b) desquamation of skin lesions over palm and soles with defervescence, starting from periungual region, and (c) development of cardiac complications.

  Cardiac involvement is the most important complication of KD due to coronary vasculitis, characterized by myocarditis and transient pericarditis in acute phase and development of coronary aneurysms and myocardial infarction in later stages.
- ***Convalescent phase*** (>4 weeks) begins with disappearance of clinical features and continues till normalization of ESR by 6–8 weeks.

Diagnosis: While early diagnosis of KD is essential to reduce the risk of coronary disease, most cases are misdiagnosed as viral fevers due to gradual evolution of clinical features and absence of a specific diagnostic test.

Diagnosis of KD in under-five children rests on a clinical criteria including the presence of—(a) unexplained fever

TABLE 24.11: Diagnostic criteria for Kawasaki disease

- **Fever persisting for > 5 days, *with***
- **At least four of the following features:**
  - Typical skin changes on peripheral extremities
    Acute: Erythema and edema of hands and feet
    Late: Periungual peeling of fingers and toes
  - Polymorphous rash, specially over trunk
  - Bilateral bulbar conjunctival injection without exudate
  - Oral cavity: Erythema, cracking lips, strawberry tongue
  - Acute non-purulent lymphadenopathy (> 1.5 cm)
- **Absence of other identifiable cause**

for >5 days, and (b) at least *four* principal clinical features in absence of alternative diagnosis **(Table 24.11)**, with following other considerations

- Presence of even less than four *principal clinical features* is sufficient for diagnosis, in cases with fever and coronary involvement.
- Children with persistent fever but < 4 principal features (in absence of alternate diagnosis) are termed as having ***Incomplete KD***, which is more common in infants <6 months or children >6 years of age.
- Patients fulfilling diagnosis of KD but with few unusual clinical manifestations, e.g. pulmonary or renal involvement are termed as having ***atypical KD***.

Thrombocytosis is common in 2–3rd week of illness and supports the diagnosis. Non-specific acute phase reactants, e.g. TLC, ESR, CRP, etc., are elevated but ANA and RF are negative.

Echocardiography in KD is essential to monitor the development of coronary vasculitis and presence of coronary artery aneurysm (CAA), indicated in all cases at the time of diagnosis, *after 1–2* weeks and again *after 4–6* weeks of treatment to detect coronary abnormalities. Some centers also advise additional screening at 1 year, though chances of late sequelae are rare if absent till 8 weeks and normalization of ESR.

While well-formed coronary aneurysms are rare in early stages, lack of the normal tapering of the vessels and enhanced coronary artery dimensions are early predictors of coronary involvement in KD, which is classified as per *Z score classification*, based on the normal internal diameter of coronary vessels adjusted for body surface area as follows: (1) *No involvement* if Z score <+2, (2) coronary dilatation if Z score 2–2.5, (3) small CAA if Z score 2.5–5, (4) medium CAA if Z score 5–10 but absolute dimension <8 mm, and (5) large/giant CAA if Z score 5–10 or absolute dimension >8 mm.

In cases with significant coronary abnormalities, repeat echocardiography is recommended at least twice a week till luminal dimensions stabilize and thereafter at 2 weeks, 4–6 weeks, 3 months, and then every 6–12 months till all parameters normalize.

D/D of KD includes—(a) exanthematous fevers, e.g. measles, (b) toxic-shock syndrome, (c) drug reactions, and (d) systemic-onset rheumatoid arthritis.

TABLE 24.12: Treatment of Kawasaki disease

Acute stage
- Single-dose IVIG 2 mg/kg over 10–12 hour, and
- High-dose Aspirin PO 80–100 mg/kg/d q6–8hr till afebrile for 48 hours

Subsequent therapy (No coronary abnormality)
- Low-dose Aspirin PO 3–5 mg/kg OD till 6–8 weeks
- Long-term therapy (with coronary abnormality)
- Low-dose Aspirin PO 3–5 mg/kg OD, with or without
- Anticoagulants, e.g. LMW Heparin or warfarin*

Acute coronary thrombosis
- Prompt fibrinolytic therapy under intensive care

LMW: Low molecular weight *in large or multiple aneurysms.

Management revolves around single dose IV immunoglobulins (IVIG) with prolonged aspirin therapy, depending on the stage of disease and state of cardiac complications **(Table 24.12)**.

While the mechanism of action in uncertain, IVIG rapidly induces resolution of fever and clinical signs as well as reduces the risk of coronary disease from 20–25% in untreated cases to <4% (only, if given within first 10 days).

About 15% cases do not respond to IVIG with persistence of fever beyond 36 hours. These cases are at higher risk of Coronary aneurysms and may be given another dose of IVIG. IVIG resistant KD may be further treated with high dose methylprednisolone or biologicals, e.g. Infliximab.

Aspirin therapy should begin with higher anti-inflammatory doses in early stage, followed by lower antithrombotic doses after patient remains afebrile for >48 hours.

Prognosis: Recovery is complete in absence of coronary involvement and recurrence is extremely rare (<1–3%). About 50% of aneurysms resolve echocardiographically by 1–2 years, though large aneurysms are unlikely to recover and may require bypass surgery or heart transplant. Overall mortality rate is <1%.

24.4.4 POLYARTERITIS NODOSA

Polyarteritis nodosa (PAN) is a rare but severe necrotizing vasculitis of small- and medium-sized arteries, although most cases present beyond childhood.

Etiology is unknown, though occurrence of PAN after viral and streptococcal infections as well in chronic HBV disease suggests probability of post-infectious autoimmune response in susceptible individuals.

Clinical manifestations are usually preceded by acute febrile illness and depend on site of involvement. Most cases initially present with unexplained pyrexia, arthralgia, myalgia and wasting, followed by system-specific features, e.g. (a) *skin involvement* with Linear purpura, edema and painful nodules along the course

TABLE 24.13: Diagnostic (Ozen) criteria for pediatric PAN

Necrotizing vasculitis* on histopathology **or**
Vascular aneurysm/stenosis/occlusion* on angiography
With any one of the following:
- Skin involvement
- Myalgia/Muscle tenderness
- Hypertension
- Peripheral neuropathy
- Renal involvement

*Of small or medium arteries
Abridged from EULAR/PRINTO/PRES criteria 2008

TABLE 24.14: Diagnostic criteria for childhood Takayasu disease

- Angiographic abnormalities, ***With***
- Any one of the following criteria:
  - Weak peripheral pulses or claudication of limbs
  - BP difference between arms or legs >10 mm Hg
  - Bruits over the aorta or its major branches
  - Hypertension
  - Elevated acute phase reactant (ESR, CRP)

Abridged from EULAR/PRINTO/PRES criteria 2010

of vessels, (b) *renal involvement* with hypertension, hematuria or proteinuria, (c) *GIT involvement* with severe abdominal pain due to mesenteric vasculitis, (d) *coronary involvement* with myocarditis, cardiomegaly or CCF, and (e) *CNS involvement* with stroke, psychosis or peripheral neuropathy.

Diagnosis rests on *Ozen criteria* **(Table 24.13)**, including either (a) biopsy of skin nodules or kidney showing signs of segmental fibrinoid necrosis of medium-sized arteries, *or* (b) angiographic studies to demonstrate aneurysms of renal or celiac vessels, along with at least one clinical feature/organ involvement.

Treatment includes long-term immunosuppressive therapy with steroids or cyclophosphamide. Course of disease depends on the severity and extent of vascular involvement.

24.4.5 TAKAYASU DISEASE

Takayasu disease (Idiopathic aortoarteritis, Pulseless disease) is a chronic vasculitis of large-sized vessels, leading to vascular obstruction and aneurysm formations.

Etiopathogenesis: While exact inciting agent for immunological injury is unknown, a similar disease has been reported in India and other asian countries in association with tuberculosis (*Tubercular aortoarteritis*).

Clinically, Takayasu disease is more common in females and usually diagnosed during adolescence.

Clinical course is progressive, presenting with:
- Unexplained hypertension and consequent complications, e.g. encephalopathy, cardiomyopathy or pulmonary edema; and
- Signs of vascular obstruction depending on the site of involvement, e.g. carotid or subclavian bruit, absent limb pulsations, lower blood pressure in legs than in arms (coarctation of aorta) and renal manifestations due to renal arterial involvement.

Rarely, other features of connective tissue diseases, e.g. arthritis, weight loss, erythema nodosum rash, etc. may be present.

Diagnosis is suspected clinically in presence of unexplained hypertension and confirmed on angiography to demonstrate site of obstruction **(Table 24.14)**. In India, all cases should also be investigated for tuberculosis, though the cause-effect relationship is uncertain.

Treatment includes: (a) anti-hypertensive therapy, (b) non-invasive balloon/stent dilatation or surgical repair of obstructive vascular lesions, and (c) immunosuppressive therapy with steroids, methotrexate or cyclophosphamide in progressive disease. Anti-tubercular therapy has been used in cases with suspected tubercular etiology, though it is unlikely to prevent progression of vascular lesions.

Prognosis depends on severity at diagnosis and further progression of disease, with 5-year mortality of ~5%, usually due to aneurysmal rupture.

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CHAPTER

25

Skin Disorders

Mukesh Agrawal

Skin disorders are common cause of parental concern, not only for primary pathologies but also for aesthetic and cosmetic reasons. Apart from a protective covering, skin also serves as sensory organ as well as participates in many physiological activities, e.g. thermoregulation, Vitamin D metabolism and energy storage.

25.1 BASIC CONSIDERATIONS

Embryologically, the skin and its appendages develop from *ectoderm.*

Anatomically, skin is the largest organ of body, containing three layers-epidermis, dermis and hypodermis (subcutaneous fat), along with its appendages **(Fig. 25.1)**.

Epidermis, the barrier layer, is a stratified epithelial tissue made up of specialized cells, i.e. keratinocytes. The deepest epidermal layer, i.e. *stratum basalis* is the germinal layer from where keratinocytes continuously develop and move superficially to mature further to form other epidermal layers, i.e. *stratum spinosum*, *stratum granulosum* and finally the most superficial layer, i.e. *stratum corneum*. Top-most layer of S. corneum contain plenty of keratin, i.e. dead keratinocytes, which are continuously shed and replaced by lower cell layers. Thus, epidermis is in a state of dynamic balance between formation of immature keratinocyte in deepest S. basalis and shedding of keratin from upper-most S. corneum-whole cycle taking about 28 days.

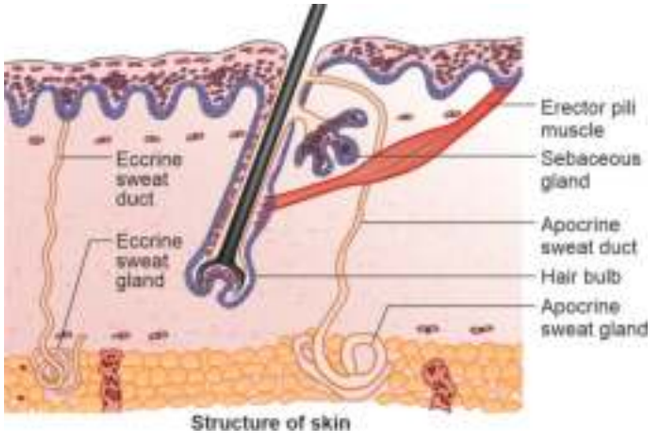

Fig. 25.1: Basic structure of skin

Other important cells in epidermis are *melanocytes* (producing melanin pigment), *Merkel cells* (related to sensory function) and *Langerhans cells* (related to immune function).

Dermis, the supporting layer, consists of collagen and elastic fibers to provide strength and resilience to skin, along with blood vessels, lymphatics, neural structures and skin appendages. Predominant dermal cell is a spindle-shaped fibroblast, which produces collagen, elastic fibers and mucopolysaccharidoses, i.e. ground matrix.

Hypodermis (subcutaneous fat) consists of fat cells (adipocytes) arranged in lobules by dividing fibrous septa and serves mainly as heat insulator or trauma protector.

Skin appendages include *hair follicles, sebaceous glands, apocrine and eccrine sweat glands* and *nails*, all present mainly in dermis.

Clinical evaluation of skin disease: While most skin disorders are easily identifiable on examination of skin lesion under adequate illumination, careful history and systemic examination is important for etiological confirmation. Many skin lesions are a part of systemic illnesses, e.g. malnutrition, vitamin deficiency or endocrinal diseases.

Clinically, skin lesions should be examined and described according to their: (a) *morphology,* (b) *size,* (c) *color,* (d) *texture,* (e) *location or distribution, and* (f) *configuration.* A commonly used descriptive nomenclature in dermatology is given in **Table 25.1** which categorizes skin lesions into *primary lesions and secondary lesions*, developing after or over primary lesions. Using these terms helps not only in differential diagnosis but also to communicate better between care providers. However, many lesions are too altered in their morphology after therapy, infection or trauma, to have a diagnostic value.

TABLE 25.1: Common descriptive terms for morphological lesions in skin diseases

Primary lesions		*Secondary lesions*	
Macules	A flat, well-circumscribed lesion of altered color, <1 cm	**Scales**	Sheet-like, compressed, unshed layer of S. corneum
Patch	A Macule of >1 cm	**Erosion**	Moist shallow lesion with focal loss of epidermis, heals without scarring
Papule	A raised lesion of altered color, <1 cm	**Ulcer**	Focal loss of epidermis and dermis, heals with scarring
Nodule	A papule of >1 cm	**Excoriation**	Linear/angular ulcers, on scratching
Tumor	A nodule of >2 cm	**Fissures**	Splitting/cracking over skin lines
Plaque	An elevated, flat-top lesion of >1 cm	**Crust**	Dried accumulation of blood, pus and cell debris, over weepy lesions
Vesicle	A raised, fluid-filled lesion, <1 cm	**Scar**	Thick, firm discolored collection of conn. Tissue, on healing
Bullae	A vesicle of >1 cm	**Lichenification**	Thickened epidermis with accentuated skin lines, due to chronic irritation/inflammation
Cyst	A fluid-filled papule/nodule with epidermal lining		
Pustule	A pus-filled vesicle <1 cm		
Blebs	A pus-filled bullae (or pustule >1 cm)		
Wheels	A raised, flat-topped, edematous papule or plaque, which is transient		
Petechiae	Bleeding* macule <2 mm		
Purpura	Bleeding* macule/papule >2 mm		
Ecchymosis	Bleeding* nodule >10 mm		
Arrangement of lesions			
Linear	Arranged in straight line	**Grouped**	Clustered lesions, e.g. HSV
Nummular	Round, coin sized lesions	**Reticular**	Lace-like arrangement
Annular	Ring-like lesions	**Dermatomal**	Localized to one or more dermatome
Iris lesions	Ring-like lesions with central clearing		

*due to extravasated blood, do not blanch on pressure (d/d macule)

Laboratory investigations: Dermatological diagnosis in difficult cases may be supported by:

- *Wood's lamp examination* (ultraviolet rays) for hypo-pigmented and fungal infections, etc.
- *KOH preparation* of skin scrapping for fungal infections
- *Tzanck smear* from presumably viral blisters, specially for chickenpox or HSV lesions
- *Skin-punch biopsy* for diagnostic confirmation in many diseases.
- *Immunofluorescence studies* to detect tissue-fixed antibodies, e.g. in pemphigus, dermatitis herpetiformis and connective tissue disorders.

Topical therapy in dermatology: Topical therapy is the mainstay of treatment in most dermatological disorders, either alone or along with systemic therapy.

Topical applicants are available in various forms, depending on specific agent (steroid, antimicrobials or keratolytic agents) and the vehicle (lotion, creams, ointments, powders and pastes). Some important concepts in topical therapy are as follows:

Vehicles: Selection of proper vehicle is as important in topical therapy as the specific therapeutic agents. *Lotions* are pourable mixture of water with some oil while *creams* are non-pourable mixtures of water with more oil. *Ointments* have either oil alone or very small amount of water. Lotions and creams are more useful for acute weepy lesions while ointments are preferable over dry, thickened and scaly lesions. *Powders* are hygroscopic vehicles and are more useful as absorptive agents in high-moisture areas, e.g. intertriginous area and groin. *Pastes* are mixtures of powders in ointment base, often used as non-specific bland agents to cover friction areas, e.g. in diaper dermatitis.

Specific therapeutic agents for topical therapy may be *bland*, e.g. wet dressing or lubricants or with *active* pharmacological properties. Some commonly used therapeutic agents in dermatology are as follows:

Wet dressing is often the initial treatment in acutely inflamed or moist oozing lesions to decrease pruritis and burning sensation. These dressings may be provided by simply dipping a soft cotton/gauze piece in normal

saline, plain water or *Burrow's solution* (2–5% aluminum acetate in water) and applying over the lesion for 10–20 minutes. Closed wet dressings are needed over abscesses.

Lubricants, i.e. bland lotions, creams and ointments and petroleum jelly, are used as vehicle for other drugs, as well as emollients for dry and pruritic skin. These preparations are most effective when applied over damp skin immediately after bath or when contain evaporation agents, e.g. camphor or menthol.

Keratolytic agents are used to soften and humidify thickened skin, for easy removal of scales and crusts. Common keratolytic agents include salicylic acid, urea and α-hydroxy acids, e.g. lactic or glycolic acid. *Whitfield ointment* (6% benzoic acid +3% salicylic acid) is a commonly used keratolytic as well as antifungal agent.

Sunscreens reflect all sunrays or selectively harmful ultraviolet rays and mainly contain zinc oxide or titanium oxide. These agents are used for prevention of photosensitive rashes or dermatitis.

Tar compounds have antipruritic and astringent properties as well as promote normal keratinization. These compounds are used for psoriasis and chronic eczema and efficacy is increased on post-application exposure to sunlight. Tar compounds should never be used on acutely inflamed lesions.

Topical antibiotics should not contain antibiotics that are commonly used for systemic therapy for fear of sensitization. Mupirocin is perhaps the most effective topical antibiotics for cutaneous bacterial infections.

Topical antifungal agents may be broad spectrum, i.e. azoles-miconazole, clotrimazole, ketoconazole or selectively acting, e.g. nystatin (candida), tolnaftate (dermatophytes), etc.

Topical steroids are potent anti-inflammatory and antipruritic agents, classified as: (a) *non-fluorinated*, e.g. hydrocortisone and mometasone, and (b) *fluorinated*, e.g. betamethasone, fluocinolone and triamcinolone. Fluorinated compounds are more potent but toxic, and should be used with caution.

Apart from vehicles and special therapeutic agents, many topical preparations contain preservatives and stabilizing agents, which may cause local allergic reactions.

25.2 DEVELOPMENTAL SKIN DISORDERS

All children have some or other developmental defects of skin, though most of them are of no clinical consequence. Some benign skin stigmata may point towards the more serious underlying problems due to common embryological insult, e.g. sacral or spinal dimple (spina bifida occulta), patellar dimple (congenital rubella), loose skin folds over neck (Turner/Noonan syndrome), pre-auricular tags or sinuses (renal anomalies), accessory tragus (Goldenhar syndrome), etc.

Some important developmental defects with primary skin involvement are as follows:

Aplasia cutis congenita, i.e. *development absence of skin*, presents as solitary or multiple, well-demarcated, non-inflammatory ulcers or atrophic scars, usually over scalp. Depth of lesion may vary from minimal epidermal loss to deep lesions involving dermis, subcutaneous tissue and rarely, the bone. Most cases are isolated skin defects, thought to be due to intrauterine vascular insult and recover spontaneously. Large or deep lesions may be complicated with hemorrhage, infection or underlying meningitis. Surgical closure is rarely required.

Amniotic constriction bands present as partial grooving or complete amputation of body parts, e.g. limbs or digits, due to premature amniotic rupture following amniocentesis or blunt abdominal injury, leading to entanglement of fetal parts in shrivelled amniotic bands. More severe craniofacial defects, may be caused by vascular disruption due to constriction bands in embryonic life **(Fig. 25.2)**.

Branchial clefts, sinuses or cysts present as lateralized* skin defects or swellings in neck, usually along the tract of second branchial arch. While some lesions are blind, others may open on the skin *or* in pharynx. Most of these lesions are asymptomatic, till complicated by secondary infections, which should be treated with antibiotics followed by surgical excision.

* Similar neck lesions in mid-line indicate *thyroglossal cyst/sinus*, which also move with deglutition.

Ectodermal dysplasia is a heterogeneous group of rare hereditary disorders involving almost all ectodermal tissues, e.g. skin, its appendages and teeth. Most cases are characterized by: (a) dry, hyperkeratinized skin,

Fig. 25.2: Amniotic constriction bands.

(b) absence of sweating, (c) hair abnormalities, and (d) abnormal dentition. Three important variants include:

a. **Anhidrotic ectodermal dysplasia** is an *X-linked recessive disorder,* with a triad of: (a) partial/complete absence of sweating due to deficiency of eccrine glands, (b) anomalous dentition, e.g. anodontia/hypodontia with conical teeth, (c) hypotrichosis with sparse hypopigmented hair, eyebrows and eyelashes. These cases present in infancy with hyperpyrexic episodes (poor sweating) and recurrent respiratory infections (paucity of mucus glands), along with typical face (dental/hair abnormalities) and dry-wrinkled skin. Most of them die by 2 years due to hyperpyrexia or respiratory infections.
b. **Hidrotic ectodermal dysplasia** *(Clouston syndrome)* is much rare and presents with dystrophic nails, sparse hair and hyperkeratosis of palm/soles; but with *normal sweating and dentition*.
c. **EEC syndrome,** an autosomal dominant disorder with variable penetrance, denotes: (a) ***E***ctrodactyly, i.e. spilt hand/feet, (b) ***E***ctodermal dysplasia with dry skin, sparse hair, dysplastic nails, but *normal sweating*, and (c) ***C***leftlip/palate.

Developmental vascular anomalies of skin may be divided into two groups: (a) *proliferative hamartomas* of vascular endothelium, e.g. hemangioma, and (b) *vascular malformations,* e.g. salmon patch, port-wine stain, etc. **(Fig. 25.3)**.

Fig. 25.3: Common hemangiomas in children: (A) Strawberry hemangioma; (B) Port wine stains; (C) Salmon patch; (D) Cavernous hemangioma.

Salmon patch (Stork-bites) are commonest vascular malformations, seen in ~40% newborns. Clinically, these lesions present at birth as small, diffuse, pale-pink telangiectatic macules over face, specially at glabella, upper eyelids and nape of the neck. Salmon patches are usually bilaterally symmetrical and tend to be more prominent during crying. Most of them fade away spontaneously by the end of first year.

Port-wine stains are permanent capillary malformations, presenting at birth as flat, well circumscribed, bright/dark red macular lesions of variable size, usually in head and neck region. Unlike Salmon patch, port-wine stains are often large, unilateral and do not involute spontaneously. Rather, these lesions become darker and nodular over time. Treatment of choice is laser ablation in early infancy, to prevent accidental bleeding.

Two important syndromes associated with port-wine stains are as follows:

- *Sturge-Weber syndrome,* i.e. facial port-wine stain with intracranial hemangioma, (Ch 18.14)
- *Klippel-Trenaunay-Weber syndrome,* i.e. port-wine stain over limbs with underlying bony/soft tissue hypertrophy and venous varicosities.

Infantile (Strawberry) hemangioma is a superficial capillary hemangioma, presenting as bright-red, well-demarcated plaque or nodule over face, scalp or upper chest. Unlike port-wine stains, these lesions are raised above the surface and can be easily blanched on pressure.

These hemangiomas are present at birth or appear soon after, and expand rapidly (and may ulcerate/bleed) during next few months, before entering into a stationary phase and subsequent regression by 5–7 years in most cases.

Considering the benign course, no specific therapy is indicated *except* in cases with: (a) deep-seated or very large lesions, (b) pressure symptoms affecting vision, feeding or respiration.

Conventional treatment for rapidly proliferating lesions has been oral steroids (Prednisolone 2–3 mg/kg/d as single morning dose) for 4–6 weeks followed by gradual tapering. Steroids are postulated to have an inhibitory effect on the production of vascular endothelial growth factor (VEGF) by stem cells. High-dose pulse methylprednisolone IV 30 mg/kg/day infused slowly for 3 days may be used for life-threatening situations, e.g. large hemangioma blocking airways.

Oral propranolol (2 mg/kg/day) for 6–9 months is emerging as preferred option in relatively stable cases, which acts by inducing vasoconstriction of feeding vessels as well as inhibition of VGEF production Response is obvious within few days with change of color and softening of lesions.

Other options in non-responders are: (a) intra-lesional steroids, (b) sclerotherapy, (c) surgical excision, and (d) laser therapy.

Kasabach-Merritt syndrome refers to a large infantile hemangioma with thrombocytopenia, microangiopathic hemolytic anemia and DIC, due to mechanical destruction of blood cells.

Cavernous hemangiomas of skin are deep-seated and ill-defined, appearing as cystic/firm, compressible lesions with normal or bluish overlying skin. These lesions also follow the same course as strawberry hemangiomas (expansion > stationary > regression). However, considering the proximity with deeper vital structures, treatment with oral steroids (as discussed earlier), sclerotherapy or surgical excision is often required.

Ichthyosis denotes a rare group of hereditary skin disorders, all characterized by abnormal keratinization or cornification of skin, i.e. *hyperkeratosis*.

Abnormal thickening of S. corneum (N:10–50 mm) and delayed shedding of keratin leads to formation of *dry adherent scales*, either all over or on selected parts of skin. Apart from cosmetic problems, this horny skin with limited elasticity also affects mobility of underlying structures, e.g. joints and muscles, leading to disfigurement and disabilities in severe cases. Itching may be present.

Ichthyosis is also the part of many autosomal recessive syndromes, e.g. *Sjören-Larson syndrome* (with mental retardation and spasticity), *Refsum syndrome* (with chronic polyneuritis and sensory organ defects) and *Rud syndrome* (with mental retardation, sexual infantilism and epilepsy).

Some important types of ichthyosis are as follows:

Ichthyosis vulgaris is the commonest (1:300) and mildest ichthyosis with autosomal dominant inheritance. While normal at birth, these cases present in early infancy with dry, rough skin and mildly pruritic scaling, usually limited to extensor aspects of limbs **(Fig. 25.4)**.

Lesions are more pronounced in winter season and tend to improve or disappear with age. Scaling may be diminished by use of bath oils and application of an emollient/lubricant with a keratolytic agent, e.g. salicylic acid.

Fig. 25.4: Ichthyosis.

X-linked ichthyosis due to steroid sulfatase deficiency, is seen only in males and present at 3–6 months with development of large dark-brown scales all over body, sparing palms and soles. Corneal opacities are common.

Harlequin fetus, most severe autosomal recessive ichthyosis is obvious at birth with marked thickening and cracking of skin, which covers the baby with horny plates and leads to severe disfigurement, e.g. ectropion, flat facial contour, limited joint mobility and breathing difficulties due to poor stretchability of skin. Most cases die in neonatal period/early infancy due to respiratory problems or excessive fluid loss from breaks in stratum corneum.

Collodion baby is an at-birth manifestation of many forms of ichthyosis (commonest lamellar ichthyosis).

Clinically, these newborns are covered with a thick, taut and oily-parchment like membrane (*collodion*) at birth, which deforms the face with ectropion, flattened nose/ears and fixed lips with open mouth. Membrane cracks with initial respiratory efforts and sheds in large sheets, revealing underlying ichthyotic (or rarely normal) skin.

Management includes nursing in high humidity environment and topical application of lubricants to facilitate membrane shedding and correction of complications, e.g. dehydration, dyselectrolytemia, aspiration and hypothermia.

Many collodion babies die in neonatal period due to aspiration of membranous material, hypothermia or dehydration (due to altered skin permeability), though final prognosis depends on the type of ichthyosis.

Ehlers-Danlos syndrome is a group of genetically inherited connective-tissue disorders, all characterised by quantitative deficiency of collagen. Depending on mode of inheritance and clinical presentation, 10 different types are known, with all or some of the following features:

a. *Hyperelasticity, fragility and easy bruisability* of skin. These cases may develop large ecchymosis and gaping ulcerations after trivial trauma, which heal with difficulty, leaving large scars and keloids.
b. *Hypermobility of joints* (hyper-gymnasts).
c. *Systemic manifestations* due to defective collagen, e.g. aneurysms, internal organ ruptures (intestines/bladder), corneal rupture, fragile bones, etc.

Most of these disorders are not fatal but morbidity may be high. Treatment is non-specific including avoidance of trauma, pregnancy (risk of uterine rupture) and surgical procedures (risk of wound dehiscence). Oral ascorbic acid (vitamin C) may be useful in some cases.

Cutis laxa is a congenital disorder of probably dermal *elastin*, characterized by marked laxity (but not elasticity)

of skin. Depending on the severity of defect, these cases present with:

a. *Premature sagging* of facial skin or loose skin folds hanging from face and neck ((senile or blood-hound appearance). *Unlike Ehlers-Danlos syndrome, skin elasticity is normal*.
b. *Systemic manifestations,* e.g. hoarse cry (vocal cord laxity), multiple hernia, rectal prolapse, recurrent emphysema and cardiac lesions, e.g. valvular dilatation/regurgitation. Most cases also have growth retardation, sexual infantilism and ligamentous laxity.

While some cases manifest at birth, others present later after febrile illnesses or allergic/inflammatory skin disorders (acquired cutis laxa). Life span may be shortened by systemic complications.

Pseudoxanthoma elasticum is a multi-systemic disorder of elastic tissue due to a genetic defect with abnormal glycosaminoglycan deposition over elastic fibers, predominantly affecting skin, eyes and vascular system.

Clinically, skin manifestations begin in childhood with characteristic linear/reticular confluent plaques of tiny yellow papules (*plucked chicken-skin appearance*), over flexural regions, e.g. neck, axilla, inguinal folds and antecubital fossa. Gradually, skin may acquire velvety texture and droops in lax, inelastic folds. Mucus membranes may be involved. Involvement of vascular connective tissue may cause cerebral/coronary occlusions in adulthood.

25.3 COMMON SKIN INFECTIONS

Skin is the primary barrier between internal milieu and external environment and hence, bears the burnt of many infective insults.

25.3.1 BACTERIAL INFECTIONS

Impetigo contagiosa (Pyoderma) is the commonest bacterial infection in children, mostly seen during hot and humid summer seasons.

Clinically, impetigo may be nonbullous (70%) or bullous.

Nonbullous impetigo, caused by β-hemolytic streptococci or *Staph. aureus,* typical begin on exposed parts of body after a breach in skin continuity, e.g. insect bite, abrasion, scabies, etc. Initial lesions appear as a tiny vesicle or pustule, which rapidly develops into a honey-colored crusted plaque without much pain/erythema. **(Fig. 25.5A)**. Satellite lesions are common due to spread of infection by fingers or fomites.

Bullous impetigo, caused by *Staph. aureus*, is mainly seen in infants and present as transparent bullae or blister, filled with turbid fluid over normal skin, mainly on face and diaper area.

Diagnosis may be confirmed by culture of the plaque or blister fluid.

D/D of bullous impetigo includes epidermolysis bullosa, herpetic infection and pemphigus.

Complications are rare and include: (a) local cellulitis, (b) regional lymphadenitis, (c) distant systemic infections, e.g. pneumonia, septicemia, arthritis/osteomyelitis, and (d) acute post streptococcal *glomerulonephritis.* Rheumatic fever is rare by dermatogenic strains of β-hemolytic streptococci.

Management: Topical mupirocin ointment thrice a day for 7–10 days is enough in most cases, though systemic antibiotics, i.e. erythromycin (30–50 mg/kg/d for 7 days) are required in cases with wide-spread lesions or local/regional complications. Alternatives, e.g. cloxacillin, amoxicillin/clavulinic acid or cephalosporins may be used in non-responders.

Folliculitis is the superficial infection of hair follicle, predominantly caused by *Staph. aureus*. Important risk factors include: Poor hygiene, moisture with maceration of skin, immunodeficiency disorders and prolonged antibiotic therapy (fungal folliculitis)

Clinically, These cases typically present over scalp, buttocks and extremities, as small, discrete, dome-shaped pustules with erythematous base **(Fig. 25.5B)**.

Treatment of folliculitis includes topical antibiotics, though severe cases may need systemic antibiotics, e.g. cloxacillin or cephalaxin.

Furuncle is a deep-seated folliculitis due to *Staph. aureus*, presenting as tender, indurated nodule in hair bearing area, e.g. face, axilla, buttocks and groin **(Fig. 25.5C)**. These nodules are intensely painful, suppurate rapidly and rupture to discharge pus before healing with scar formation.

Carbuncle is the folliculitis of many contagious follicles with surrounding cellulitis and multiple drainage points. Carbuncles are common in obese, diabetic, malnourished or immunodeficient children.

Management include: (a) hot, moist compresses over closed lesions to facilitate drainage, (b) incision and drainage of large lesions, and (c) systemic cloxacillin or cephalosporin for large furuncles or carbuncles.

Erysipelas is an acute deep-seated *streptococcal* skin infection with lymphangitis involving face or extremities. It presents as well-defined, indurated, erythema with raised, firm borders and superficial vesiculations **(Fig. 25.5D)**. High dose IV penicillin (2–4 Lac units/kg/d q8hr) with/without clindamycin is the treatment of choice.

Cellulitis is a deep-seated infection of subcutaneous connective tissue, due to *S. pyogenes* or *Staph. aureus.* Lesion is similar to erysipelas but with ill-defined margins **(Fig. 25.5E)**. Constitutional features and complications, e.g. abscess and bacteremia are common. Mild cases may

Fig. 25.5A to L: Common skin infections: (A) Impetigo; (B) Folliculitis; (C) Furuncle; (D) Erysepelas; (E) Cellulitis; (F) Scrofuloderma; (G) Tinea versicolor; (H) Tinea corporis; (I) Mucocutaneous candidiasis; (J) Warts; (K) Herpes zoster; (L) Herpes simplex*

be treated with PO cloxacillin or cephalosporin, while severe cases may need parenteral antibiotics.

Staphylococcal scalded skin syndrome is the most serious staphylococcal skin infection with generalized vesiculobullous lesions, discussed later in Ch 25.6.

Skin tuberculosis may present as: (a) *erythema nodosum*—a hypersensitivity manifestation, (b) *scrofuloderma*, (c) *tuberculids,* or (d) *lupus vulgaris*.

Lupus vulgaris, rare in children, presents as solitary, well-defined, reddish-brown plaque with atrophic center and centrifugal spread of lesion. Apple-jelly nodules are seen on pressing the lesion with a clean glass slide.

Scrofuloderma, due to contagious spread from a tubercular sinus, presents as serpiginous lesions with undermined margins surrounding the sinus **(Fig. 25.5F)**.

25.3.2 FUNGAL INFECTIONS

Tinea versicolor is a common, innocuous chronic fungal infection in adolescents, caused by a yeast, *Malassezia furfur.*

Predisposing factors, e.g. hot, humid environment, excessive sweating and steroid therapy leads to proliferation of disease-producing filamentous form.

Clinically these lesions present as non-pruritic, confluent hypo/hyperpigmented patches over neck and upper trunk **(Fig. 25.5G)**.

Diagnosis may be confirmed by wood's lamp examination (yellowish-gold fluorescence) and KOH preparation of scrapping.

Management includes topical application of selenium sulfide, salicylic acid or antifungal creams (e.g. miconazole, clotrimazole or ketoconazole) for 2–4 weeks, though lesions tend to recur in predisposed children and may require oral antifungal therapy.

Dermatophytoses (Ringworm) is a group of clinical fungal infections caused by three related filamentous fungi-*Trichophyton, Microsporum and Epidermophyton.* Infection is acquired from other humans, animals or directly from soil. Though common in even normal children, infection tends to be more severe in children with diabetes, high-steroid states, e.g. Cushing syndrome or steroid therapy, and immunosuppression.

Clinically these infections are named according to the site of lesion like *Tenia captis* (scalp), *T. corporis* (anywhere on body except palm, soles and groin), *T. cruris* (groin), *T. pedis* or athlete foot (toe webs) and *T. ungium* (nails).

Most tenia lesions begins as a tiny papule over the base of a hair follicle and spreads centrifugally with central clearing (*ringworm*) to form erythematous, scaly and pruritic plaques with brittle/broken hair over them **(Fig. 25.5H)**.

Established cases of T. captis often present with multiple pruritic patches of alopecia over scalp. Similar lesions are seen in T. corporis and T. cruris, later being more common in adolescent males. Unlike candidiasis, *penis is almost always spared in T. cruris*.

T. ungium presents as irregular white patches over nails, sometimes associated with paronychia. Later, the nail becomes brittle and discolored, which may crack or break-away from nail-bed.

Diagnosis is clinical, supported by microscopic examination of wet KOH preparation for spores and occasionally by culture of broken hair, skin scrapping or nail on *Sabouraud* media.

D/D includes alopecia areata, seborrheic dermatitis and trichotillomania (for T. capitis), nummular eczema, tinea versicolor and pityriasis rosea (for T. capitis), intertrigo, candidiasis and contact dermatitis (for T. cruris), atopic dermatitis, contact dermatitis, candidiasis and intertrigo (for T. pedis) and dystrophic nail disorders or nail trauma (for T. ungium).

Management: Topical antifungal therapy with miconazole, ketoconazole or clotrimazole twice daily for 2–4 weeks is usually enough for T. corporis, T. cruris and T. pedis. Cases with groin or pedal lesions should avoid use of tight innerwear/footwear.

For T. capitis or severe T. corporis, oral antifungal therapy with Griseofulvin (15 mg/kg/d) or itroconazole (3–5 mg/kg/d) for 6–8 weeks is necessary, along with vigorous shampooing (2.5% selenium sulfide) for scalp lesions. Oral Terbinafine (3–6 mg/kg/day) for 4–6 weeks may also be used in older children > 4 years.

T. ungium is most difficult to treat as topical therapy or oral griseofulvin is ineffective. Itroconazole (PO 6–10 mg/kg/d) for 7 days in a month for 4–6 months is the treatment of choice in these cases.

Cutaneous candidiasis is not uncommon in newborns and in older children during hot/humid climate, though extensive, refractory or systemic disease indicates underlying immunodeficiency.

Clinically, skin lesions are common over moist and macerated skin, presenting as cheesy-white plaques over intensely erythematous skin/mucosa, specially over flexural regions, e.g. diaper region **(Fig. 25.5I)**, axilla, intertriginous region, vagina and nails (candidal paronychia).

Diagnosis may be confirmed by scrapping and KOH preparation.

Management: Topical antifungal therapy (clotrimazole, nystatin, miconazole) is enough for most cases, though a short course of topical steroids is indicated in acutely inflamed cases. Oral antifungal therapy with nystatin is needed in refractory or recurrent candidal lesions or nail infections.

25.3.3 VIRAL INFECTIONS

Common warts (Verruca vulgaris) due to *human papillomavirus* (HPV-2 and 4) are seen in ~5–10% of all children at some point of time, though more common in immunocompromised states, e.g. HIV.

Clinically, warts appear as well-circumscribed papules with rough, keratotic and irregular surface, mainly over fingers, dorsum of hand and knees **(Fig. 25.5J)**. Paring away of the papule reveals many black dots representing thrombosed dermal capillary loops. Warts are rarely painful except when on pressure areas, e.g. soles or palms. Genital warts are rare in children except in early infancy due to passage from infected birth canal or in sexually active adolescents.

Treatment: Over 50% warts disappear spontaneously within 2 years, but infection may spread to other sites. Large disfigurative lesions may be destroyed by keratolytic therapy (daily application of 10% salicylic acid/lactic acid in a collodion) for 2–4 weeks, cryotherapy (liquid nitrogen application for 6–9 seconds) or light electro-dessication.

Molluscum contagiosum due to pox-virus (mainly type 1) is not uncommon in school-children, though recurrent or multiple lesions indicate immunocompromised state, e.g. HIV. Infection is acquired by direct contact with an infected person or fomites and spreads by autoinoculation.

Clinically, these lesions are discrete dome-shaped, skin-colored papules (1–5 mm) with typical central umbilication, from which a plug of cheesy material can be expressed. Lesions are more common over face, eyelids, neck, axilla and thighs. HIV-infected children tend to have large and numerous lesions.

Treatment: While molluscum contagiosum is self-limiting (6–9 months), infective nature and risk of spread by auto-inoculation demands early treatment with cryotherapy (treatment of choice) or expression of plug by a sterile needle, curette or comedo extractor.

Herpes zoster due to reactivation of previous varicella infection is rare in children, except in immunocompromised hosts. Recurrent or multidermatomal herpes zoster is considered as an AIDS-indicator illness.

Clinically, these cases present as sudden eruption of grouped vesicular lesions over an erythematous patch, with typical *dermatomal distribution* **(Fig. 25.5K)**. New vesicles may continue to erupt for next 3–5 days, while older vesicles dry and crust, which fall after 10–14 days leaving a hyperpigmented lesion. Prodromal pain and post-herpetic neuralgia is rare in children.

Treatment: Although lesions are self-limiting, oral acyclovir therapy is indicated in most cases, starting as early as possible, specially in severe disease or underlying immunodeficiency.

Herpes labialis is a common and usually recurrent manifestation of dormant HSV1 infection after many years of clinical or latent primary disease. Lesions are often precipitated by a febrile illness (herpes febrilis), viral infection or cold stress.

Clinically, these lesions present as grouped, small, clear vesicles on an erythematous base, usually over upper/lower lip **(Fig. 25.5L)**.

Treatment: While most cases are mild and self-limiting, topical application of 5% acyclovir cream in early eruptive phase may reduce severity or duration of attack.

25.3.4 PARASITIC INFESTATIONS

Pediculosis capitis (head lice) is the commonest parasitic skin infestation in Indian children, while other types, e.g. P. corporis (body lice) and P. pubis (groin lice) is uncommon.

Etiologically P. capitis is ~2–4 mm in length, transmitted by head-to-head contact or through shared comb or towels. Female lice lives for about 1 month and lays 3–10 eggs/day. Eggs glue to the proximal part of hair shaft and hatch to form larvae that feeds on human blood along with adult lice—injecting their salivary juices into host and depositing fecal matter over skin (responsible for itching). Nits are empty sacs of chitin left behind on hair shaft after hatching and migration of larvae.

Clinically, *pruritus* is the hallmark of infestation, though secondary pyoderma over scalp are common in children. On examination, nits are easily visible than the lice and may be differentiated from dandruff by its firm attachment with hair shaft.

Treatment of choice for killing adult lice/larvae is the single application of Permethrin 1% cream on wet hair for 10 minutes followed by head wash and repeated after 7 days. Other options include similar application of Gamma benzene hexachloride 1% for overnight or Malathion 0.5% for 6 hours, both on dry hair, which may also be repeated after 7–10 days.

Nits may be removed by fine-tooth combing after rinsing the hair with 1:1 vinegar. Other important steps include treatment of all family members sharing common bed, hot-water washing of cloths/bed linens and regular shampooing of hair.

Scabies is the second commonest parasitic infestation of skin after pediculosis, mostly seen in slum children living in overcrowded and unhygienic slums.

Etiologically, it is caused by burrowing and release of toxic or antigenic substances by the female mite *Sarcoptes scabiei*. Infestation is transmitted by close physical contact with an infested family member, and rarely by fomites. After impregnating the skin, gravid female exudes a keratolytic substance to burrow under S. corneum and deposit eggs and fecal pallets (scybala). Although she dies in 4–5 weeks after burrowing, eggs hatch and mature in next 2–3 weeks to restart the cycle.

Clinically lesions appear after about one month of infestation, presenting with pruritus, particularly at night, and tiny (1–2 mm) red papules over the burrowed site that may crust, excoriate or get infected to form vesiculopustular lesions **(Fig. 25.6)**. While any part of body may be affected in infants/toddlers, lesions are more common over inter-digital spaces, wrist and flexural regions in older children sparing head, neck, palm and soles.

Complications include: (a) eczematous dermatitis, (b) superimposed pyoderma, folliculitis, cellulitis, and (c) regional lymphadenopathy.

Diagnosis may be made clinically on history and visualization of *burrows* with a magnifying lens, while confirmation requires microscopic examination of scraping from these burrows or papules to demonstrate adult mite, ova or scybala. Other family members are frequently co-infected.

Treatment includes application of a scabicidal agent from neck to toe (also on face, neck and scalp in infants) after a scrub bath. Treatment should be repeated after a gap of 7–10 days in severe cases.

While Benzyl benzoate 25% (for 3 days) or Gamma benzene hexachloride 1% (single application) are commonly used for this purpose, a single application of Permethrin 5% is the preferred choice in children >2 months, to avoid burning sensation on benzyl benzoate application and potential neurotoxicity of gamma benzene hexachloride. Scabies in infants < 2 months may be treated with Crotamiton 10% two applications daily for 14 days.

Oral Ivermectin 0.2 mg/kg is an effective alternative for infected scabies in older children > 3 years.

Other important components of scabies treatment are simultaneous treatment of all family members (even if asymptomatic) and washing of patient's clothing and bed-linens with hot water. Antihistaminics may be used for symptomatic relief from pruritus. Despite effective treatment scabies tend to be recurrent in susceptible population, unless proper hygiene is maintained.

Fig. 25.6: Scabies: (A) Hand; (B) Inter-digital region.
(*Courtesy:* Dr Uday Khopkar)

25.4 PIGMENTARY SKIN DISORDERS

Normal skin pigmentation depends on the melanin production by melanocytes, which are mainly present in epidermis and synthesize melanin from tyrosine-an amino acid. Melanocytes are derived from neuro-ectoderm and migrate to epidermis in embryonic life. Pigmentary disturbances may be congenital **(Table 25.2)** or acquired; and clinically present as generalized or localized (patchy) hypo/hyperpigmented lesions.

25.4.1 HYPERPIGMENTED LESIONS

Hyperpigmentation denotes increased melanin production and/or deposition in epidermis (brownish black) or dermis (bluish-black), presenting either as isolated skin lesions or as a part of systemic disease **(Table 25.3)**. Common hyperpigmented lesions in children are as follows:

Café-au-lait spots are dark-brown, well-demarcated, macular lesions of variable size (*see* **Fig. 18.17**), present at

TABLE 25.2: Common pigmentary lesions at birth

Color/Lesion	*Diagnosis*	*Common location*	*Association*
Brown macule/patch	Café-au-lait spots	Trunk	Neurofibromatosis
Brown plaque	C. melanocytic nevus	Trunk, scalp	Hypertrichosis, melanoma
Flesh-colored plaque	Epidermal nevus	Trunk, neck	–
Red patch	Port-wine stain	Face	Sturge-Weber syndrome
Red papule/plaque	Hemangioma	Head and neck	Airway lesions
Red vesicular plaque	Lymphangioma	Trunk, legs	–
Blue patch	Mongolian spots	Buttocks, back	Fade in childhood
Blue plaque	Venous malformation	Anywhere	Enlarges over time
Blue nodule	Dermoid cyst	Head and neck	CNS dermoid
Yellow plaque/nodule	Xanthogranuloma*	trunk	–
White patch	Nevus depigmentosus	Anywhere	–

*or mastocytoma, which may blister

TABLE 25.3: Common hyperpigmented skin lesions

- **Primary skin lesions:**
  - *Epidermal:* Café-au-lait spots, freckles, lentigines
  - *Dermal:* Mongolian spots
  - *Mixed:* Post-inflammatory, incontinentia pigmenti
  - *Melanocytic nevi:* Congenital or acquired
- **Secondary to systemic disease:**
  - Addison disease
  - Kala-azar
  - Infantile tremor syndrome

birth or appear later on. Although these spots are present in ~10% of normal children, two important syndromes associated with many or large-sized café-au-lait spots are:

- *Neurofibromatosis* (Chapter 18.14), associated with > 5 spots of >5 mm; and
- *McCune Albright syndrome* with large asymmetrical café-au-lait spots of irregular borders, polyostotic fibrous dysplasia of bones, precocious puberty and multiple endocrinopathies.

Ephelides or freckles are brown macules of <3 mm, commonly seen in school children over *sun-exposed parts,* e.g. face, upper back and arms/hands. These lesions tend to appear in summer and fade in winter season. Except for a possible association with melanoma, these lesions are essentially benign.

Lentigines, though appearance-wise similar to freckles, these lesions may develop on any part of body, unrelated with sun exposure and remain permanent. Multiple lentigines may be indicative of *Addison's disease* or *Peut-Jeghers syndrome* (with GIT polyposis).

Mongolian spots are bluish/grayish flat patches (confused with bruises) of variable size mainly over sacral area and upper thighs **(Fig. 12.6)**. These spots, seen in ~80% of newborns, represent presence of melanocytes in dermis, due to incomplete migration from neural crest to epidermis in embryonic life. Mongolian spots usually fade away in later life and are of no clinical consequence.

Melanocytic nevi, an abnormal but benign clustering of normal melanocytes usually at epidermal-dermal junction, may be congenital in 1% newborns or acquired usually during or after adolescence. Congenital melanocytic nevi are usually larger than acquired lesions and carry a small risk of developing melanoma in later life. Malignant transformation is extremely rare in acquired nevi.

Congenital giant pigmented nevi (>20 cm), most commonly seen over back are of special significance due to frequent association with leptomeningeal melanosis and predisposition for subsequent malignant transformation. Clinically, these lesions are asymptomatic or present with neurological manifestations, e.g. hydrocephalus, mental retardation and/or seizures. MRI of brain is essential in all cases. Local excision and grafting reduces the risk of secondary melanoma but at the cost of disfigurement.

25.4.2 HYPOPIGMENTED LESIONS

Primary hypopigmented lesions are caused by congenital or acquired deficiency in number of melanocytes and hereditary defects in tyrosine metabolism, though similar lesions are also seen in fungal infections **(Table 25.4)**. Some common hypopigmentary disorders are as follows:

Albinism, a *congenital* hypopigmentation disorder, denotes "*complete or partial failure of melanin production in skin, hair and/or eyes, despite the presence of normal number, structure and distribution of melanocytes*".

Etiologically, albinism is caused by many hereditary enzyme defects at different stages of tyrosine metabolism, responsible for biosynthesis or distribution of melanin.

Clinically, Albinism may be generalized or localized and severity may vary according to the enzymatic defects, though common manifestations include: (a) generalized or partial hypopigmentation of skin, hair and/or eyes, *since birth,* (b) decreased visual acuity, photophobia and strabismus, with red-eye reflex due to translucent Iris **(Fig. 25.7A)**. Skin cancer and complete blindness are late complications in most severe forms of albinism and albinism-associated syndromes. (Ch 11.6.1)

Management is non-specific, including: (a) protection from sunlight to prevent skin cancers by protective clothing, sun screens, sun glasses and caps, (b) correction of refractive errors, and (c) genetic counseling.

Vitiligo is an *acquired* (d/d albinism) and usually patchy depigmentary disorder, due to reduced or absent melanocytes.

Etiopathogenesis is unclear, though most probably involves increased destruction of melanocytes due to *autoimmune* or other unknown factors. Family history is present in 30–40% cases and many cases are associated with systemic autoimmune disorders, e.g. Addison's disease, pernicious anemia, thyroid disease, etc.

Clinically, most pediatric cases present after first decade of life with well-demarcated milky-white or

TABLE 25.4: Common hypopigmented skin lesions

Generalized:		
Congenital	:	Oculocutaneous albinism
Acquired	:	Universal vitiligo
Localized:		
Congenital	:	Partial albinism and associated syndromes
Acquired	:	Vitiligo
		Leprosy
		Fungal skin infections
		Pityriasis alba
		Post-inflammatory lesions

Fig. 25.7: **(A) Albinism; (B) Vitiligo.**

hypopigmented patches, usually over normally hyperpigmented areas, e.g. face, axilla, groin and areola or friction-prone areas, e.g. distal extremities and joints **(Fig. 25.7B)**. Vitiligo may be localized, segmental or generalized. Course of vitiligo is variable, with spontaneous re-pigmentation in 10–20% cases.

Diagnosis is clinical *or* on skin biopsy. Common D/D of vitiligo includes leprosy (sensory loss), albinism (congenital) and leukoderma (a non-progressive patch after burns or local inflammatory lesions.

Management: Reassurance regarding its benign nature is most important, considering social stigma attached to vitiligo. Management depends on the site and size of lesions and success rate is variable despite prolonged therapy.

Common modalities for small patches include: (a) topical steroids, e.g. fluocinolone acetonide or calcineurin inhibitors, e.g. Tacrolimus, (b) topical PUVA therapy in children above 10 years, and/or (c) cosmetic tattoo or skin grafting. Large lesions need systemic PUVA therapy. Systemic steroids are used to arrest progression of rapidly spreading lesions.

PUVA therapy consists of topical or systemic administration of psoralen (a plant-derived chemical, furocoumarins) followed by ultraviolet radiation to stimulate melanocyte function and regeneration. However, it is contraindicated in young children due to higher risk of skin cancers.

Pityriasis alba is the commonest hypopigmented skin lesion in children with unknown etiology, though often regarded as a mild form of eczema. Unlike general belief, it has no relation with calcium or iron deficiency.

Clinically, it is characterized by hypopigmented, round or oval, macular or slightly elevated patches with fine adherent scale and ill-defined margins over face, neck, upper chest and shoulders **(Fig. 25.8)**. Itching is minimal or absent. Lesions are exacerbated by dryness and often run a waxing-waning course for many months before disappearing completely.

Fig. 25.8: **Pityriasis alba.**

Diagnosis is clinical, though needs to be differentiated from T. versicolor or T. corporis by KOH preparation of skin scrapping.

Management: These are very benign and self-limiting lesions except cosmetic apprehension. Application of a lubricant or topical steroid (hydrocortisone 1%) thrice a day is often enough to ameliorate the lesion, though normal pigmentation may return after many months.

25.5 MACULOPAPULAR DISORDERS

Maculopapular lesions are commonest skin rashes, seen either as *primary* lesions or as the *earliest* lesions in other evolving rashes, *e.g.* vesiculobullous lesions.

Primary maculopapular lesions may be seen in isolated skin disease *or* as cutaneous manifestation of infective (exanthematous fevers) or non-infective systemic illnesses **(Table 25.5)**. Some important causes of maculopapular lesions with primary skin involvement are as follows:

Miliaria rubra (Prickly heat) is the commonest cause of macular eruptions during hot and humid season, caused by occlusion of eccrine sweat ducts by a keratin plug. Clinically, it presents as erythematous, itchy, 1–3 mm macules all over body, specially forehead, neck, upper chest and back. Rupture of sweat-glands due to back pressure may lead to leakage of sweat in epidermis/dermis with inflammatory changes and secondary infection. Local cold compresses are effective to control itching, while regular bath may prevent them.

TABLE 25.5: Causes of maculo-papular rash

- **Primary skin lesions**
  - Hypersensitivity rash
    - Urticaria
    - Insect bites
    - Drug reactions
    - Photosensitive rash
  - Primary skin infections
    - *Bacterial:* Evolving pyoderma
    - *Fungal:* T. versicolor, candida
    - *Viral:* Molluscum contagiosum
    - *Parasitic:* Scabies, pediculosis
  - Miliaria rubra
  - Evolving rash in other skin lesions
- **Maculopapular lesions in systemic disease**
  - Infections (Exanthematous fevers)
    - *Viral:* Measles, rubella, dengue
    - *Bacterial:* Scarlet fever, enteric fever
    - *Spirochetal:* Congenital syphilis
    - *Rickettsial:* Epidemic/endemic typhus
    - *Parasitic:* Malaria, toxoplasmosis
  - *Collagen disorders:* SLE, dermatomyositis
  - *Nutritional diseases:* Pellagra
  - *Miscellaneous:* Histiocytosis

Miliaria crystallina (Sudamina rash), is another variant of miliaria, is commonly seen in febrile states *or* poor hygiene, with sudden eruption of asymptomatic, non-inflammatory, pin-point, extremely superficial and clear *vesicles*, which leave brawny desquamation on healing after 2–3 days.

Drug eruptions: Cutaneous manifestations of drug reactions vary widely, commonly presenting as exanthematous rashes, urticaria/angioedema, fixed drug eruptions, photosensitive rash, vascultis and very severe lesions, e.g. Steven-Johnson syndrome (Chapter 25.6). Most of them are caused by drugs antibiotics, anticonvulsants, NSAIDs, and vaccines.

Morbilliform (Exanthematous) drug eruptions are common after exposure to penicillins or cephalosporins, specially ampicillin. *Clinically*, these rashes present as acute onset of measles-like generalized macules with or without pruritis, most prominent of chest and proximal extremities. Unlike measles, these rashes are not associated with fever and rarely last for more than 48 hours. Antihistaminics decrease the itching but do not alter the course of eruptions.

Fixed drug eruption, though relatively uncommon in children, present as dusky-red macules after exposure to an offending drug (cotrimoxazole, NSAIDs, ciprofloxacin) that rapidly turn bluish-black and persist for many months **(Fig. 25.9)**. *Characteristic feature of these lesions is the recurrence of lesion at the same site after subsequent exposures to the drug*. No specific treatment is effective except topical steroids in acute phase and avoidance of drug.

Fig. 25.9: Fixed drug eruption.

Insect bites: Insect-related skin reactions are produced by direct contact or actual bite, due to numerous household or wild insects, e.g. mosquitoes, bees, wasps, bedbugs, spiders and mites, etc.

Clinically, the severity of reaction depends on species of insect, age of child and reactivity of skin. While severe generalized reactions *or* urticaria may be seen in newborns and hypersensitive children, most older children respond with transient and mild reactions, limited to local papule or wheal formation. Insect bites are typically: (a) seen on exposed parts of body, (b) often pruritic, (c) limited to few lesions, and (d) usually transient.

Urticaria (Hives) is the commonest cutaneous hypersensitivity reaction to any exogenous, endogenous or unidentifiable allergen **(Table 25.6)**, representing an *IgE-mediated* immune response. Urticaria may be acute or cronic, *i.e.* episodic attacks for >6 weeks. Unlike acute urticaria, chronic urticaria is usually idiopathic, though anti-IgE antibodies are present in ~25–50% cases.

Clinically, these cases present with wide clinical spectrum, ranging from localized pruritic macule

TABLE 25.6: Precipitating factors for urticaria

- **Exogenous**
  - *Inhalants:* Pollens, animal danders
  - *Ingestants:* Drugs, food, coloring agents
  - *Injectants:* Insect bites/stings, drugs
  - *Contactants:* Insects, mites, dust, danders
- **Endogenous**
  - *Infections:* Helminthiasis, viruses, malaria
  - *Illnesses:* Cholestasis, SLE
  - *Vasogenic:* Heat/cold urticaria, sun exposure
  - Hereditary angioedema (C3 inhibitor deficiency)
- **Idiopathic**

Fig. 25.10: Urticaria.

to severe angioneurotic edema. Typical urticarial lesions begin as *pruritic* macules or patches, which rapidly enlarge to form coalescing wheels **(Fig. 25.10)**. Characteristically, these lesions do not last for >48 hours, though new lesions may continue to appear. *Dermographism,* i.e. excessive wheal-flare response on stroking of the skin is common.

Angioneurotic edema is the most severe variant of urticaria involving dermis as well as subcutaneous tissue (d/d urticaria involving only dermis) with marked edema of affected parts, e.g. eyelids, lips, scrotum, limbs and sometimes, potentially fatal laryngeal edema. Severe anaphylactic reactions and bronchospasm may develop in some cases.

Diagnosis of urticaria/angioedema is largely clinical, based on: (a) presence of marked pruritis, (b) transient and often recurrent lesions, (c) family history of atopy in many cases, and (d) onset after exposure to a known allergen in some cases. Laboratory investigations may reveal eosinophilia and/or raised IgE levels in some cases. *In vitro* skin allergen tests are unreliable. Collage vascular disorders should be excluded in chronic urticaria.

Management depends on the severity of lesion. *Mild or localized cases* may be treated on outdoor basis with oral antihistaminics, cold compresses or topical antipruritic lotions. S*evere cases*, e.g. *angioneurotic edema* need hospitalization to supervise for complications, e.g. laryngospasm, bronchospasm or anaphylaxis; and treated with intensive supportive measures, parenteral adrenaline, steroids and antihistaminics.

While drug and foods are most common causes of urticaria in children, some other important types of urticaria are as follows:

- **Papular urticaria**, seen mainly in early childhood during summer season denotes more diffuse response to common insect bite (*id reaction*), presenting as widely distributed urticarial or maculopapular lesions all over body in different stages of evolution, even after quiescent bites or minimal local reaction.
- **Cold urticaria,** i.e. appearance of urticarial lesions on exposure to cold weather or local application of cold (ice, bath, swimming) may be *primary* or *secondary.* Secondary cold urticaria is usually seen in adults with cryofibrinogenemia, cryoglobulinemia, cold-agglutinin disease, etc. Primary cold urticaria usually appears and disappears spontaneously, sometimes after a viral illness.
- **Episodic urticaria** with fever and eosinophilia has been described as a separate clinical entity in children and adults, which unlike other hypereosinophilic syndromes, runs a benign course.
- **Solar urticaria** presents with generalized wheal and flare reaction after 5–10 minutes of sun exposure that fades after 1–2 hours. Headache, syncope and/or bronchospasm is common during the attack. *Primary solar urticaria* probably indicates a type I hypersensitivity to some irradiation-induced allergen, while *secondary solar urticaria* is due to photosensitization by various drugs, chemicals or metabolites (*see* photosensitive rashes).

Photosensitivity rash: Some children are extraordinarily sensitive to sun exposure, either due to their normal skin type (sunburns, hypopigmentary disorders) or presence of abnormal drugs/metabolites in skin (photoallergic/phototoxic reactions). Many other skin disorders, albeit of different etiology, may be exacerbated on light exposure **(Table 25.7)**. Some important photosensitive rashes are as follows:

Acute sunburn is the commonest photosensitive reaction in fair-skin children, due to direct effect of ultraviolet

TABLE 25.7: Causes of photosensitive rash

- **Acute sunburns** (direct effect of ultra-violet light)
- **Photoallergic/phototoxic reactions**
  - *Drugs:* sulfonamides, barbiturates, NSAIDs
  - *Chemicals:* Cosmetics, perfumed oils, tars
  - Phytophotodermatitis*
  - *Nutritional:* Pellagra
  - *Metabolic errors:* Porphyria, hartnup disease
- **Genetic photosensitivity syndromes**
  - Xeroderma pigmentosum or cockayne syndrome
  - Bloom syndrome
- **Hypopigmentary disorders**
  - Albinism
  - Vitiligo
- **Skin diseases exacerbated by light exposure**
  - *Collagen disorders:* SLE, dermatomyositis
  - Solar urticaria
  - Atopic dermatitis
  - *Others:* Pemphigus, psoriasis

*due to consumption of psoralen containing fruits and plants
NSAIDs: Non-steroidal anti-inflammatory agents

radiations (290–320 nm) in sunlight. Children vary in their susceptibility to sunburns, depending on their skin color, i.e. amount of pigment. Sunlight radiations <300 nm are usually absorbed by epidermis and melanin, whereas that of >300 nm are transmitted to dermis, causing sunburns.

Clinically, sunburns manifest after 6–12 hours of exposure as redness, tenderness, edema and skin blistering with peak effect at ~24 hours. After prolonged or repeated exposures, enhanced melanogenesis may reduce skin sensitivity to sunburns. Unduly prolonged and intense sun exposure may lead to premature aging *or* increased risk of skin cancers, e.g. malignant melanoma.

Local cold compresses, topical steroids and anti-inflammatory agents are useful in acute phase, while further damage may be prevented by avoidance of sun exposure and use of protective clothing and sun-screens.

Photoallergic vs Phototoxic reactions: Presence of various photosensitizers in skin/circulation, e.g. drugs, chemicals or metabolites **(Table 25.7)**, may provoke photosensitive dermatitis on exposure to certain wave lengths of light.

- *Photoallergic reactions* are T-cell mediated hypersensitivity reactions to photosensitizers, which require prior sensitization, seen only in selected individuals and are not dose-related.
- *Phototoxic reactions* are dose-related, seen in all individuals after sufficient dose-intake and prior sensitization is not required.

Genetic photosensitivity disorders are rare, usually autosomal recessive and include: (a) increased propensity to chromosomal breakage on exposure to ultraviolet rays, e.g. Bloom syndrome, (b) defective nucleotide excision-repair, e.g. Xeroderma pigmentosum, and (c) accumulation of photosensitive metabolites in inborn errors of metabolism, e.g. porphyria, Hartnup disease.

Xeroderma pigmentosum is a rare defect in nucleotide excision-repair, characterized by: (a) skin manifestations, e.g., photosensitive dermatitis and tendency for skin malignancies, (b) ocular manifestations, e.g., photophobia, keratitis, etc. and (c) neurological manifestations, e.g. mental retardation or sensorineural deafness in ~20%.

Cockayne syndrome, a variant of xeroderma pigmentosum, presents in late infancy with: (a) photosensitive *butterfly facial rash* on sun-exposure with secondary changes, (b) short stature, (c) facial dysmorphism, i.e. large ears, pinched nose and premature graying of hair, (d) intellectual disability, (e) limited joint mobility, (f) progressive deafness, and (g) ocular lesions, e.g. cataracts and retinal degeneration. Neurological manifestations due to extensive demyelination develop soon and most patients die in late adolescence due to premature atherosclerosis.

Bloom syndrome is a rare disorder with increased propensity for chromosomal breakages on ultraviolet rays exposure. Clinically, these cases present in infancy with: (a) photosensitive *butterfly facial rash*, (b) short stature, (c) facial dysmorphism, with small, narrow face with prominent nose and ears, (d) tendency for lymphoreticular malignancies. Susceptibility to infections due to hypogammaglobulinemia is common. Other skin lesions, dental and digital abnormalities, e.g. polydactyly may be present.

25.6 VESICULOBULLOUS DISORDERS

Vesiculobullous (blistering) eruptions are seen in many systemic illnesses, e.g. exanthematous fevers, e.g. varicella or primary skin disorders, e.g. infections, hypersensitivity reactions, autoimmune or hereditary disorders, etc. **(Table 25.8)**.

Differential diagnosis depends on the age, morphology/distribution of lesions, precipitating factors and presence of coexisting mucosal/systemic involvement. Family history indicates hereditary disorders, e.g. epidermolysis bullosa.

Skin biopsy to determine the depth of blisters is an extremely valuable in diagnosis of vesiculo-bullous disorders, which may be broadly divided into following categories:

a. *Intracorneal* or *subcorneal* blisters, e.g. miliaria, candidiasis, are very tiny, fragile and easily missed. Some cases present only as desquamated skin.
b. *Intra-epidermal blisters*, e.g. infections, pemphigus, etc. are usually flaccid, easily ruptured and heal without scarring. *Niklosky sign*, i.e. lateral extension of lesion on pressure is positive in some cases.

TABLE 25.8: Causes of vesico-bullous eruptions

- **Infections**
  Bacterial: Impetigo, staphylococcal scalded skin syndrome
  Viral: Chickenpox, HSV, VCZ, hand-foot-mouth syndrome
  Others: Inf. scabies, Hookworm*, Rickettsial pox
- **Hypersensitivity**
  Erythema multiforme
  Steven-Johnson syndrome
  Toxic epidermal necrolysis
- **Autoimmune**
  Pemphigus/pemphigoid
  Dermatitis herpeteformis
- **Hereditary**
  Epidermolysis bullosa
  Porphyria tarda
  Incontinentia pigmenti
- **Extrinsic factors**
  Burns, insect bites
  Miliaria

*at the site of skin entry.
HSV: Herpes simplex; **VCZ:** Varicella zoster

c. *Sub-epidermal blisters,* e.g. Steven-Johnson syndrome and its variants, are tense, thick-walled and more durable. Some important vesiculobullous disorders with primary skin involvement are as follows:

Staphylococcal scalded skin syndrome (SSSS, Ritter syndrome), is almost always seen in infants or children below 5 years of age, presenting with a spectrum of clinical manifestations ranging from localized bullous impetigo to generalized skin lesions with systemic involvement.

Etiologically, SSSS is caused by epidermolytic or exfoliative exotoxins of phage group 2 *staphylococci* (strain 71, 55), usually infecting nasopharynx, umbilicus or superficial abrasion.

Clinically, a typical case presents with:

a. *Prodromal phase* with fever, malaise, irritability and extreme tenderness all over the skin for few hours;
b. *Exfoliative phase,* beginning as a generalized macular or erythematous rash, specially in flexural or periorificial region that rapidly evolves to form ill-defined bullae/blisters filled with clear fluid. Skin surrounding the bullae separates easily by gentle finger pressure (*Nikolsky sign*). Peeling of large sheets of epidermis leaves behind denuded, moist areas **(Fig. 25.11)**, with complications, e.g. secondary infection and fluid-electrolyte imbalance.

   Circumoral erythema and radial crusting/fissuring around eyes, nose and mouth is characteristic in SSSS, though intra-oral lesions are absent. Pharyngitis and conjunctivitis is common as also systemic infections, e.g. septicemia or pneumonia.
c. *Desquamative phase* begins after 2–5 days, healing the ulcers without scarring.

Atypical cases may present with localized bullous impetigo *or* generalized erythema without blister formations.

Diagnosis rests on typical evolution and distribution of lesions with *positive Nikolsky sign*, confirmed on skin biopsy to show *intra-epidermal plane of cleavage* and characteristic absence of inflammatory infiltrate. Intact bullae/blisters are essentially sterile, though cultures from suspected sites, e.g. throat may reveal source of toxin production.

Treatment of these cases includes:

a. *Systemic antibiotic therapy* with IV/PO penicillinase-resistant penicillin, e.g. cloxacillin or amoxicillin/clavulanic acid.
b. *Local care:* Gentle moistening and cleaning of skin with normal saline followed by application of bland emollient ointment (topical antibiotics are useless, unless secondary infection is present).
c. *Treatment of complications,* e.g. fluid and electrolyte imbalance or systemic infection, e.g. pneumonia, septicemia, etc.

Steven-Johnson syndrome (SJS) is the commonest and prototype manifestation of *acute vesicobullous hypersensitivity reactions* to various infections, drugs or other agents **(Table 25.9)** in young children below 10 years of age.

Other uncommon presentations include *Erythema multiforme* and *Toxic epidermal necrolysis,* discussed later, which share a common pathogenesis but with variable severity and age of presentation.t

Clinically, SJS is often preceded by mild viral respiratory illness and characterized by rapidly progressive involvement of skin and at least two mucus membranes, **(Fig. 25.12)** as follows:

a. *Generalized skin lesions,* which begin as tender, dusky, erythematous macules and progress rapidly with central necrosis to form vesicles, bullae and large denudated areas over face, trunk and extremities. New lesions appear in crops for next 1–2 weeks.
b. *Mucosal involvement* of at least *two* of the following sites: (a) eyes with conjunctivitis or keratitis/corneal ulcers, (b) oropharynx with edema, erythema, ulceration, crusting and burning sensation, (c) anogenital mucosal lesions, and (d) internal mucosal lesions manifesting as cough, diarrhea/dysentery or hematuria.
c. *Secondary complications* in acute phase include: (a) dehydration due to insensible fluid loss from

Fig. 25.11: Staphylococcal scalded skin syndrome.

TABLE 25.9: Causes of Steven-Johnson syndrome

- **Infections:**
  - *Viral:* HSV, EBV, HBV, enteroviruses
  - *Bacterial:* Streptococci gr A, tuberculosis
  - Mycoplasma pneumoniae
- **Drugs:**
  - *Anticonvulsants:* Phenytoin, Phenobarb, Carbamazepine
  - *Antibiotics:* Sulfonamides*, penicillin, isoniazid
  - *Others:* NSAIDs, captopril, radiotherapy
- **Neoplasia:** Leukemia, lymphoma
- **Miscellaneous:** Photosensitivity, pregnancy

*commonest cause.

Fig. 25.12: Steven-Johnson Syndrome: (A) Mucosal Lesions; (B) Skin Lesions.
(*Courtesy*: Dr Uday Khopkar)

lesions, (b) superadded local infection or septicemia, (c) satellite infections, e.g. bronchopneumonia, arthritis, panophthalmitis, myocarditis, hepatitis, etc.

d. *Self-limiting course* with complete healing in 4–6 weeks, though rare late complications include: (a) corneal scarring and visual impairment, and (b) bronchial/esophageal/anal/vaginal strictures.

Diagnosis is clinical, supported by history of drug exposure or preceding viral illness. Skin biopsy reveals *sub-epidermal plane of cleavage*.

Management is largely supportive, including:

- IV Fluid and electrolyte correction in acute stage.
- Nutritional support with IV fluids or oral feeds. Topical anesthetics, e.g. lidocaine jelly may be used before feeds to facilitate oral feeding.
- Systemic antibiotics for secondary infections.
- Cleaning of denuded areas with saline/Burrow's solution compresses and paraffin/hydrogel dressings.
- Eye-care with antibiotic or moistening eye drops.
- Steroids are not routinely recommended though a short course of high-dose steroids may be useful in severe disease with deeper mucosal lesions.

Erythema multiforme (EM), is more common hypersensitivity reaction in older children >10 years. HSV infection has been implicated in 60% cases of EM and nearly all cases of recurrent EM.

Clinically, primary lesions in EM are described as *target (bulls-eye) lesions*, i.e. papules with erythematous margins, inner pale ring and central necrosis. *Unlike SJS,* EM is distinguished by:

- Lesions largely limited over extensor aspects of upper limbs, usually sparing face and trunk.
- Rarity of mucosal involvement except buccal mucosa. However, ~25% cases may present only with mucosal lesions without skin lesions.
- Absence of prodromal symptoms.
- Shorter course with complete resolution in two weeks, without sequelae.

Treatment is supportive as for SJS, though prophylactic acyclovir therapy for 6 months may be beneficial in cases of recurrent EM following HSV infection.

Toxic epidermal necrolysis (TEN) or *Lyell syndrome*, is most severe and potentially fatal hypersensitivity reaction, though relatively uncommon in childhood.

Clinically, it is characterized by:

- Widespread blister formation, followed by full thickness skin loss in sheets and positive *Nikolsky sign*. However, mucosal lesions are less severe.
- Marked constitutional toxicity with fulminant progressive course and frequent complications, e.g. shock and septicemia.
- Absence of target lesions (d/d erythema multiforme)

Diagnosis is confirmed on skin biopsy that reveals *full thickness epidermal necrosis*. D/D mainly involves SSSS, which is common in infants and lesions often spare mucosa, palm and soles.

Management of TEN needs to be more intensive, as for the burns or SJS. Systemic steroids are of no use.

Pemphigus vulgaris is an autoimmune disorder with high IgG titers against an epidermal intercellular substance-a glycoprotein desmoglobin III. Although an acquired disorder, P. vulgaris may also be seen at birth in neonates born to mothers with pemphigus.

Clinically, it is characterized by:

- Large flaccid bullae on *non-erythematous* base (d/d SJS), with *positive Nikolsky sign*, mostly over pressure points, face, groin and axilla. Blisters rupture and enlarge peripherally leaving large denuded areas with slow healing.
- Waxing and waning course, often leading to malnutrition, debility and terminally, the death.

Diagnosis rests on skin biopsy showing intradermal cleavage and characteristic anti-desmoglobin IgG antibodies on immunofluorescent staining.

Treatment: High-dose systemic steroid therapy is the treatment of choice, though some cases need cytotoxic therapy with methotrexate, cyclophosphamide or azathioprine.

Other forms of pemphigus are rare in children.

Chronic bullous disease of childhood is a IgA mediated blistering disorder, common in children <5 years with itchy, tense bullae of erythematous lesions, usually grouped around orifices, e.g. perioral, perinasal, perianal regions or in lower abdomen and buttocks. New lesions appear around previous lesions (*String of pearl appearance*). Disease is self-limiting after 2 years. Mild cases may be treated with dapsone, while severe cases required oral steroids.

Dermatitis herpetiformis, most commonly seen in 2–7 years age group, is characterized by:

a. Symmetric, grouped, *intensely pruritic* papules or vesicles (pleomorphic) sparing mucus membranes, mainly over knees, elbows, shoulders and buttocks. Lesions often mimic scabies, popular urticaria, insect bites or eczema.
b. Sub-epidermal blistering on skin biopsy.
c. Unknown etiology, though autoimmune pathology is suspected due to close association with Gluten sensitive enteropathy and HLA B-8 in >75% cases.

Treatment includes oral sulfapyridine or dapsone (most effective), local anti-pruritic agents and gluten-free diet.

Epidermolysis bullosa (EB) is group of *congenital/hereditary* disorders with variable clinical severity and inheritance pattern, the common denominator being development of blisters after minor trauma that exacerbate during warm weather and heal with/without scarring.

Clinical spectrum spans from mild autosomal dominant disease (*EB simplex*) without mucosal involvement or scarring to potentially fatal *(Junctional EB)* or severely deforming *(dystrophic EB)* variants of autosomal recessive origin. Skin biopsy reveals sub-epidermal blistering.

Epidermolysis bullosa simplex, the commonest variant, usually manifests at birth or soon after, with recurrent development of blisters over scalp and dorsal extremities, which heal without scarring. Mucosal involvement is rare. Blisters may be precipitated by minor trauma or warm weather. Secondary infections are common. Propensity to blister decreases with age.

Therapy is largely supportive including-avoidance of trauma, local care, topical antibiotics and management of systemic complications. Although blisters should be drained by puncturing, the top should be left intact to protect underlying skin.

Incontinentia pigmenti is a rare X-linked dominant disorder, which may be fatal in males.

Clinically, these cases present with three stages:

- *First stage* manifests in newborns with typically linear and erythematous streaks/plaques of vesicles on limbs and trunk. Lesions usually resolve by 3–4 months, leaving dry, hyperkeratotic verrucous plaques for next 4–6 months. Intermittent recurrence during febrile episodes is common. Eosinophilia is present in >50% cases.
- *Second stage (hyperpigmentary stage)* is the hallmark of disease, characterized by development of hyperpigmented whorls, linear streaks or patches over trunk, axilla and groin. These lesions follow *or* overlap the first stage and persist till adolescence before fading.
- *Third stage (hypopigmentary stage)* with hairless, hypopigmented, anhidrotic patches/streaks especially on flexor aspects of legs/arms, is uncommon in childhood but may overlap second stage.

Other ectodermal lesions, e.g. alopecia or dental anomalies are seen in ~80% cases, while neurological manifestations, e.g. mental retardation, seizures, etc. and/or ocular lesions, e.g. cataracts, optic atrophy, etc. are present in ~30%.

Diagnosis is largely clinical, supported by wood-lamp examination for pigmentary abnormalities. Skin biopsy of blistering lesion reveals intra-epidermal cleavage.

Management includes treatment of non-cutaneous abnormalities (skin lesions are benign) and genetic counselling.

25.7 PAPULOSQUAMOUS DISORDERS

Papulosquamous disorders are characterized by presence of scales over the underlying plaque of patch. Some important papulosquamous disorders are as follows:

Psoriasis is a chronic autoimmune papulosquamous disorder, with ~1/3rd cases manifesting in childhood. Pediatric cases are more common in females and ~50% have positive family history.

Etiopathogenesis is multifactorial. Trauma and drugs are known to precipitate/worsen skin lesions, in genetically predisposed individuals. Association with some HLA types (HLA-CW6) is known.

Clinically, these cases are characterized by chronic *relapsing-remitting* course with:

a. Erythematous papules/plaques with sharp demarcated borders, changing into thick silvery-white scales. Lesions are common over scalp, knees, elbows and lower trunk, often with symmetrical distribution **(Fig. 25.13)**.
b. Positive *Auspitz sign,* i.e. pinpoint bleeding on removal of scales.
c. Positive *Koebner response,* i.e. appearance of new lesions at the site of trauma, e.g. scratching.

Fig. 25.13: Psoriasis.

Based on morphology of lesions, psoriasis is classified as *chronic plaque psoriasis, guttate psoriasis ands pustular psoriasis*.

Diagnosis is clinical though needs to be differentiated from other papulosquamous disorders, e.g. pityriasis rosea, seborrhoeic dermatitis and lichen nitidus/striatus/planus.

Management *i*s mainly palliative, including:

- Avoidance of skin trauma.
- Topical steroids for localized plaques in early disease.
- Local application of 5–10% coal tar with/without ultraviolet or natural sun-light exposure is the treatment of choice for stable but established lesions. Local keratolytic agents (1–3%) or topical *Calcipotriene* (a vitamin D analogue) may also be used.
- *PUVA therapy* with oral/topical psoralen and ultraviolet-A radiation for severe disease is effective but not safe in children. Other options for severe disease include methotrexate, cyclosporine and oral retinoids (*Acitretin*) therapy.

Seborrheic dermatitis in childhood is most common during infancy or adolescence. It is a chronic inflammatory disease of unknown etiology, though excessive perspiration, sebaceous gland dysfunction and infection with *M. furfur* have been implicated in etiology.

Clinical picture is variable, characterized by a relapsing-remitting course. Re-activation is common during stress or due to poor hygiene.

Infants tend to have more severe and widespread disease with: (a) diffuse brawny scaling (*cradle cap*) or localized thick oily, yellowish crusts over scalp, occasionally involving eyelids and eyebrows, and (b) greasy, scaly, erythematous and non-pruritic popular dermatitis over face, neck, behind the ears, axilla and groin, with post-inflammatory dyspigmentation **(Fig. 25.14)**.

Fig. 25.14: Seborrheic dermatitis.

In adolescents, lesions are usually limited to scalp, intertriginous area and external auditory canal. In severe cases, seborrheic plaques may be eczematous and intensely erythematous.

Management includes: (a) regular use of anti-seborrheic shampoo (selenium sulfide), (b) topical steroids over acute lesion, and (c) topical antifungal ointment for *M. furfur* in some cases.

Pityriasis rosea is a common, benign papulosquamous disorder of probable viral in origin, seen mainly in young children.

Clinically most cases present after a *preceding viral prodrome*, with:

- *A herald* (mother) patch, i.e. solitary large (1–10 cm) round/oval lesion with raised border and fine adherent scales, followed after 5–10 days by
- Widespread symmetrical small (<1 cm) eruptions in crops, beginning from trunk and proximal extremities, which are raised, pink/brown in color and covered with a fine scale. Long axis of lesions corresponds with skin-cleavage lines, producing typical *Christmas tree pattern*.
- Self-limiting course with resolution in 2–6 weeks and no recurrence.

Treatment is not necessary for asymptomatic cases, though a bland emollient/lubricant lotion or topical steroids and antihistaminics may be used for itching.

Lichen planus is a common chronic dermatosis in adults, but rare in children, who account for <5% cases.

Etiologically it is considered as a T-cell mediated autoimmune disorder against unknown skin proteins. Onset of eruptions has been associated with exposure to some drugs.

Clinically, primary lesion in lichen planus is an intensely pruritic, flat-topped, polygonal and violaceous papule with fine whitish reticulations (*Wickham striae*) over the surface. These lesions are more common on flexor aspect of wrists, knee, anterior shins and tip of the penis. *Koebner phenomenon* (lesions induced by scratching) is common.

Orogenital mucosal involvement with lacy white papules is present in ~50% cases, though nail involvement is rare in children. Other variants include bullous, annular, linear and hypertrophic lichen planus. Lesions usually resolve after 12–15 months, but chronic course with intermittent exacerbations is common in older cases.

Treatment includes the use of systemic antihistaminics for pruritis and topical/ systemic/ intralesional steroids. Extensive lesions may benefit with narrow-band ultraviolet B radiation.

Lichen nitidus in more common in children and young adults, presenting with tiny 1–2 mm monomorphic hypopigmented or flesh-colored papules with a shiny surface over arms, chest, abdomen and penis, often with

linear arrangement. Spontaneous disappearance after ~1 year is common, though a mid-potent topical steroid or tracrolimus may be used to relieve pruritis.

Gianotti-Crosti syndrome is a rare papular acrodermatitis in early childhood (1–6 years), usually associated with Hepatitis B infection. Eruptions begin as acute, multiple, tiny, lichenoid papules, which later coalesce to form plaques. Lesions are more common on face, buttocks and extremities, typically *sparing the torso*. Apart from moderately severe pruritis, the children are generally well and lesions resolve spontaneously after 2–8 weeks.

25.8 ECZEMATOUS SKIN DISORDERS

Eczema is a generic term to denote many *hypersensitive skin disorders of heterogeneous etiology* **(Table 25.10)**, all characterized by:

- Typical weeping *or* oozing skin lesions, and
- Chronic course with intermittent exacerbations.

During acute phase, lesions are intensely pruritic and erythematous with microvesicle formation, while chronic lesions are typically dry and scaly with coarse skin markings (*lichenification*) and altered pigmentation.

Some important eczematous disorders are as follows:

Atopic dermatitis is the commonest eczematous disorder in children with intermittent exacerbations and remissions, related to IgE-mediated cutaneous hypersensitivity.

Pathogenesis: Three important factors in causation or progression of atopic dermatitis are:

a. *Intrinsic hyperreactivity of the skin*, as evident by family history of atopy or *white dermatographism*, i.e. wheal and flare response on stroking the skin.
b. *IgE-mediated allergic response*, with intense pruritis in acute phase, followed by chronic inflammatory reaction. Introduction of a food-allergen, e.g. egg in early infancy has been implicated as a risk factor for sensitization.
c. *Secondary infections* during acute stage and lichenification of lesions during remission.

Clinical manifestations vary according to the age and phase of the disease. A typical case is characterized by:

a. Onset of skin lesions at 2–3 months of age, coinciding with introduction of certain foods in diet, e.g. animal milk, eggs, etc.
b. Intensely pruritic, erythematous weepy patches on cheeks, face, neck and extensor surface of extremities. Secondary infection is common **(Fig. 25.15)**.

TABLE 25.10: Causes of eczema

- Atopic dermatitis
- Contact/irritant dermatitis
- Seborrheic dermatitis
- Pityriasis alba
- Nummular eczema
- Dyshidrotic eczema

Fig. 25.15: Atopic dermatitis.

c. Resolution of skin lesions by 1–2 years of age, followed by *intermittent exacerbations and remissions.*

Children with recurrent lesions develop lichenification, hyperpigmentation and scaling of earlier lesions with a whitish-hue on the face due to edema and blanching (*mask-like face*) and accentuated lines under the eyelids (*Atopic pleat, Dennie's lines, Morgan's fold*).

In older children, flexural regions, dorsum of hands/feet, eyelids and neck are more frequently affected. In some, lesions remain localized as *nummular eczema,* i.e. coin-shaped, pruritic vesicular lesions **(Fig. 25.16)**. Lasting remission usually occurs after fourth decade of life.

Diagnosis is largely clinical (***Hanifin and Rajka criteria***), based on presence of *at least three* of the following *major criteria*:

1. Typical morphology and distribution of lesions,
2. Presence of Pruritis,
3. Chronic or relapsing course, and
4. Family or personal history of atopy;

and, supported by any three of the many of the minor features listed below:

- Early age of onset (below 2 years),

Fig. 25.16: Nummular eczema.

- Skin involvement with *any* of the following-xerosis, ichthyosis, palmar hyperlinearity, pityriasis alba, white dermatographism with delayed blanching, perifollicular accentuation, non-specific hand/foot dermatitis, Tendency for staphylococcal/HSV skin infections, Nipple eczema, Facial erythema/pallor, Cheilitis and Dennie-Morgan infraorbital folds;
- Accentuation of itching when sweating,
- Ocular lesions, e.g. recurrent conjunctivitis, anterior subcapsular cataracts, keratoconus,
- Immediate skin-test reactivity or elevated serum IgE levels

D/D of atopic dermatitis includes: (a) other causes of eczema **(Table 25.10)**, (b) scabies, and (c) skin manifestations of systemic diseases, e.g. acrodermatitis enteropathica, histiocytosis, Wiskott-Aldrich syndrome, phenylketonuria, etc.

Management depends on the clinical phase:

- ***Acute phase*** with intense pruritis and inflammation is treated with topical wet dressings (*Burrow's solution*), antibiotics, e.g. mupirocin and low-potency steroids, along with oral antihistaminics. Systemic steroids should be avoided, though systemic antibiotics may be required in presence of secondary infections.
- ***During remissions,*** management aims to prevent dryness of skin by regular baths with lukewarm water for 5–10 minutes followed by immediate application of bland moisturizers, e.g. oil, creams, etc. after bath, to seal the skin moisture. Potential triggering factors, e.g. frequent hand wash with soaps or chemicals, use of acrylic cloths and exposure to house dust mite must be avoided. Dietary restrictions are unlikely to be useful and Vaccinations are not contraindicated.
- ***Chronic lichenified lesions*** may be managed with frequent (4–6 times) application of emollients after a lukewarm bath, with/without a short course of topical low-potency steroids or immunomodulators, e.g. tacrolimus, for significant pruritis. Antihistamines may also be used to break itching-scratch cycle. Narrow-band ultraviolet radiation or systemic immunosuppressive therapy may be rarely needed in extensive or resistant cases.

Contact dermatitis is a chronic skin reaction to various contactants, which may be *immunological* (Allergic contact dermatitis) or *non-immunological* (Irritant contact dermatitis) in origin.

Allergic contact dermatitis is a *T-cell mediated* hypersensitivity reaction (d/d IgE mediated atopic dermatitis), provoked by even transient contact (d/d irritant contact dermatitis) with an antigen or hapten. As initial sensitization takes few days, dermatitis develops only after persistent or re-exposure to same allergen.

Common examples of allergic contact dermatitis include: (a) *ear-lobe dermatitis* to metal earrings, (b) *rhus dermatitis* to plant, e.g. poison ivy, congress-grass, etc, (c) *apparel-dermatitis* to fabric dyes, fibers and elastics, and (d) *cosmetic-dermatitis* to powders, lipstick and nail polish.

Fig. 25.17: Irritant contact dermatitis: (A) Diaper dermatitis; (B) Saliva dermatitis.

Clinically, allergic contact dermatitis is characterized by erythematous, intensely pruritic weepy lesion, usually localized at the site of contact. Persistent/recurrent contact leads to development of typical eczema.

Management includes: (a) elimination of offending agent, (b) treatment of acute lesions with cool compresses, topical steroids and oral antihistaminics, (c) systemic steroids in severe reactions for 1–2 weeks, and (d) systemic antibiotics in secondary infections. Desensitization is not very effective in children.

Irritant contact dermatitis is caused by *prolonged* contact with endogenous irritants, e.g. saliva (over lips in habitual lip smackers), sweat (over feet after wearing tight shoes), urine (diaper dermatitis) or exogenous irritants (soaps, etc.)

Clinically, these lesions are characteristically localized and well-demarcated at the site of contact and usually begin as confluent erythema before turning into eczematous lesions over a period of time. Presence of red-satellite pustules indicates superadded candidal infection **(Fig. 25.17)**.

Management includes: (a) avoidance of possible contact, e.g. wet diapers, (b) topical application of barrier agents, e.g. petroleum jelly/zinc oxide paste after cold compresses, and (c) topical short-acting steroids (1% hydrocortisone) in selected cases, though they increase risk of superadded candidal infection.

Dyshidrotic eczema is common in summer-season, characterized by recurrent crops of intensely pruritic, non-inflammatory small vesicles, over palm, soles and lateral aspects of fingers. Secondary infection is common due to scratching. Chronic lesions appear as thick, fissured plaques.

Exact etiology is unknown, though many cases have family history of atopy or hyperhidrosis. Treatment includes wet dressings and topical steroids in acute phase and topical steroids with a lubricant and keratolytic agent during chronic phase. Hands should be protected from chemicals, harsh soaps and exposure to adverse weather.

25.9 DISORDERS OF DERMIS

While developmental dermal disorders, e.g. Ehler-Danlos syndrome, Cutis laxa, etc. have been discussed in Ch 25.2, important acquired disorders of dermis are as follows:

Keloids (hypertrophic scars) are sharply demarcated benign nodular lesions, formed over healing site, due to overgrowth of collagen tissue. Presence of many keloid lesions indicates possibility of *Ehler-Danlos syndrome* or *Rubinstein-Taybi syndrome*. Large keloids may be treated with surgical excision or intra-lesional steroid injections.

Erythema nodosum is a skin hypersensitivity reaction to infections, drugs or unknown etiology **(Table 25.11)**.

Clinically these lesions present as tender, reddish, deep seated nodules of variable size (1–10 cm), mostly over shin of tibia bilaterally. Nodules gradually turn bluish over 1–2 weeks and disappear by 3–4 weeks leaving a brownish hyperpigmentation.

No treatment is necessary except NSAIDs for relief of pain, though effort should be made to identify etiology.

Striae cutis distensae are thin, depressed, silvery and smooth bands of atrophic skin, usually seen lower abdomen and thighs. These lesions are caused by over distension and stretching of skin during periods of rapid growth, e.g. adolescence or during pregnancy, obesity, ascites, Cushing syndrome, etc. and may become less conspicuous with time.

Scleredema adultorum, may begin in late childhood, with sudden onset of brawny, non-pitting edema of the face and neck that rapidly spreads to thorax and arms. Abdomen and legs are usually spared. The face acquires a waxy, mask-like appearance *but* with normal skin color. Active phase lasts for 4–8 weeks followed by gradual spontaneous resolution, though recurrence is common. Over 70% of these cases are preceded by streptococcal or viral infections. Skin biopsy reveals increased dermal thickness due to swelling of collagen bundles and increased mucopolysaccharide content.

TABLE 25.11: Causes of erythema nodosum

- **Infections:**
  - *Bacterial:* Streptococci, leptospirosis, diphtheria
  - *Mycobacteria:* TB, leprosy
  - *Viral:* HSV, EBV, enteroviruses
  - *Parasitic:* Toxoplasmosis, filariasis, helminths
  - *Others:* Syphilis, systemic fungal infections
- **Drugs:**
  - *Antibiotics:* Sulphonamides
  - *Anticonvulsants:* Phenytoin
  - *Others:* Aspirin, oral contraceptives
- **Systemic disorders:**
  - *Autoimmune:* JIA, Crohn's disease, sarcoidosis
  - *Malignancies:* Leukemia

EBV: Epstein-Barr virus; **JIA:** Juvenile idiopathic arthritis

25.10 DISORDERS OF SUBCUTANEOUS FAT

Some important disorders of subcutaneous fat are as follows:

Panniculitis is the inflammation of subcutaneous fat due to non-infective causes, presenting as *local nodules* (poststeroid therapy, post-injection site, SLE, α-1-antitrypsin deficiency, etc.) or *large, hard plaques* (cold exposure, sclerema neonatorum and subcutaneous fat necrosis, etc.)

Subcutaneous fat necrosis, due to saponification of subcutaneous fat, is usually seen in asphyxiated newborns. Clinically, it presents as rubbery, erythematous or violaceous plaques/nodules over fatty areas, e.g. cheeks, buttocks, thighs, etc. It involutes spontaneously after many weeks/months without scarring. Hypercalcemia may be associated in these cases.

Sclerema neonatorum is a bad prognostic indicator, typically seen in critically sick newborns, specially with sepsis or hypothermia. Clinically, it is characterised by diffuse, woody induration of the skin, most prominent over face and bony points. In severe cases, face assume mask-like appearance with restriction of joint mobility. Outcome depends on primary illness.

Unlike subcutaneous fat necrosis, histopathology in sclerema neonatorum is characterized by hypertrophy of fat cells with increased intracellular spaces, without any evidence of inflammation.

Lipodystrophy may be generalized or partial and congenital *or* acquired.

Congenital generalized lipodystrophy is an autosomal recessive disorder, characterized by progressive loss of subcutaneous and visceral fat since early infancy with other skin manifestations, e.g. Hirsutism, prominent veins, etc. and systemic manifestations, e.g. voracious appetite, accelerated skeletal/muscle growth, cardiomyopathy and mental retardation. Hyperlipidemia, hyperinsulinism and insulin-resistant diabetes is common in older children.

Acquired generalized lipodystrophy with similar presentation is known in older children following viral infections *or* unexplained illnesses, perhaps due to autoimmune destruction of adipose cells.

Partial lipodystrophy is more common and may be idiopathic or secondary, e.g. insulin lipoatrophy.

Idiopathic partial lipoatrophy is more common in females, presenting in late childhood with gradual symmetrical loss of subcutaneous tissue, predominantly from face and trunk (*Cadaver face*). Exact cause is unknown, though some cases have chronic renal disease or abnormal lipid profile.

Insulin lipoatrophy develops after 1–2 year of insulin therapy, presenting as well-circumscribed dimple at the

site of injections. Cross reactivity of insulin antibodies with adipose cells is implicated in etiology, though lesions may be prevented by rotation of injection sites.

25.11 DISORDERS OF SKIN APPENDAGES

Skin appendages include hair follicles and hairs, sebaceous glands, apocrine glands, eccrine sweat glands and nails, all, except the nails, mainly present in dermis.

25.11.1 HAIR DISORDERS

Hair-follicle is a cup-like invagination of epidermis into dermis, present all over skin except over palm and soles. Human hair consists of a bulbous root at the bottom of hair follicle and a keratinized shaft. Hair growth is cyclical, with a growing phase (anagens) and resting phase (telogens). Hair follicles, if destroyed, can't regenerate again. Androgens are major determinant of secondary hair growth during puberty.

Hair abnormalities may be *intrinsic* or *secondary* to inflammatory dermatosis, biochemical/metabolic or endocrinal defects *or* traction trauma.

Hypertrichosis (excess hair growth) or *Hirsutism*, i.e. androgenic hair pattern in females, may be due to: (a) familial tendency, (b) endocrinal disorders, e.g. Cushing syndrome, virilizing tumors, (c) drugs: steroids, minoxidil, etc. or (d) genetic errors, e.g. mucopolysaccharidoses. Local hypertrichosis (tuft of hair) is seen in spina bifida occulta or hairy nevi.

Alopecia (hair loss) *or* hypotrichosis (deficient hair growth) may be partial or total, due to many factors **(Table 25.12)**. True familial alopecia is rare in children.

Mechanical alopecia in children includes *Traction alopecia* (due to tight braids, head-bands or curlers), *Pressure alopecia* (due to constant pressure in bed-ridden patients or normal infants) and *trichotillomania*.

Alopecia areata denotes rapid or complete loss of hair in round/oval patches over scalp, though rare variants include *alopecia totalis* (complete hair loss over scalp) or *alopecia universalis* (complete hair loss over scalp and body). Nearly 60% cases are children and adolescents < 20 years of age.

TABLE 25.12: Causes of Alopecia* in children

• Familial	Usually in males
• Mechanical	Traction/pressure alopecia
	Trichotillomania
• Toxic	Chemo/radiotherapy
• Nutritional	PEM, zinc deficiency, Vit. A excess
• Hereditary	MKHS, cartilage-hair dysplasia
• Inflammatory	T. captis, atopic eczema
• Autoimmune	Alopecia areata, SLE
• Structural defects	Trichorrhexis, pili torti

*Or abnormally sparse, brittle and hypopigmented hair
MKHS: Menkes-Kinky-Hair syndrome.

Exact etiology is unknown, though it has been found to be associated with emotional stress, similar family history, Down syndrome and autoimmune disorders.

Treatment is often ineffective, though topical steroids or topical minoxidil may be used in localized lesions. Extensive lesions may benefit from oral steroids or PUVA therapy.

Prognosis is unpredictable but spontaneous resolution may occur after 6–12 months in mild cases.

Trichotillomania is characterized by compulsive pulling, twisting or breaking of hairs, usually in mentally retarded or psychiatrically abnormal (obsessive-compulsive neurosis) children, leading to irregular and incomplete hair loss mostly in parietal region. *Trichobezoar,* i.e. accumulation of hairs in stomach is common in these cases.

Intrinsic structural defects of hair mainly include *Trichorrhexis nodosa,* i.e. dry, brittle, lustreless hair with multiple fractures of hair shaft presenting as grayish white nodes on shaft due to a congenital defect or wrong combing technique; and *Pili torti,* i.e. spangled, brittle and coarse hair of different length over entire scalp.

Menkes-kinky-hair syndrome, a rare x-linked recessive disorder of copper metabolism is characterized by short, fine, brittle, light-colored hair along with progressive psychomotor retardation and hypopigmented skin.

25.11.2 SEBACEOUS GLAND DISORDERS

Sebaceous glands are saccular dermal structures to produce *sebum*, which usually drains into hair follicle via sebaceous ducts. Sebaceous secretions are androgen dependent, most prominent during puberty and fetal life (constitute vernix caseosa along with desquamated s.corneum). Sebaceous lands are mainly present over face and upper chest *and* absent over palm and soles.

Acne vulgaris is a very common disorder of sebaceous glands in adolescents, characterized by recurrent pathognomonic lesions (*comedones*) with/without secondary papules, pustules or nodulo-cystic lesions.

Etiopathogenesis: Acne denotes blockade of sebaceous ductal openings into hair follicular canal, leading to distension and rupture of sebaceous glands and microbial degradation of sebum. Though exact cause is not established, four factors are important:

a. Sebaceous gland hypertrophy and increased sebum production in adolescence due to androgenic hormones.
b. Abnormal keratinization of follicular epithelium (? hereditary or hormonal), blocking sebaceous ducts by a keratin plug.

c. Back pressure in sebaceous ducts, leading to distension and rupture of sebaceous glands into dermis with inflammatory reaction and secondary lesions
d. Contributing microbial degradation of sebum—a lipoid substance, by colonizing flora of sebaceous follicles, i.e. *Propionibacterium acne*, anaerobic diphtheroids and *Staph. epidermidis.*

Pathognomonic *Comedone* is a non-inflamed dilated follicular sac filled with keratinized material and sebum.

Clinically, acne is most common in adolescents, in males, in persons with oily/hyperhidrosis skin, during hot and humid weather and in pre-menstrual phase.

Comedones appear as tiny papules (1–3 mm) with a central dot denoting pilosebaceous orifice on skin. These lesions are of two types—*open comedones or black heads*, where blackish keratin plug is visible through open and patulous pilosebaceous orifice and *closed comedones or white heads*, where follicular opening is visible only as a tiny whitish dot in the center of macule.

Secondary lesions are inflammatory, due to rupture of sebaceous glands, microbial degradation of sebum and external trauma, e.g. pinching or scratching, presenting as papules, nodules, pustules or nodulocystic lesions.

As sebaceous glands are concentrated over face and upper chest, most lesions are also seen in these regions. Most lesions heal with minimal transient scarring and hyperpigmentation, unless secondary changes are present.

Management: Acne is not preventable (except perhaps by *Tretinoin*), though lesions may be controlled and scarring may be prevented by judicious use of following measures:

a. *Regular cleansing* of skin with mild soap/water and avoidance of greasy creams or oil applications. Squeezing of comedones should be strictly avoided, as it may rupture sebaceous ducts to induce inflammation.
b. *Topical therapy* for minimum 4–6 weeks with:
   – *Comedolytic agents*, e.g. benzyl peroxide or tretinoin. *Tretinoin*—a retinoic acid derivative, is the most effective drug for non-inflammed comedones, by reducing keratinization in sebaceous follicles. It should be applied as 0.025–0.5% cream/gel once a day after face wash, starting with low concentration.
   – *Topical antibiotics*, e.g. clindamycin 1% or erythromycin 2% for inflamed lesions, to inhibit growth of *P. acne*. Simultaneous use of comedolytic agents improves penetration of these drugs.
c. *Systemic antibiotic therapy* with erythromycin or tetracycline is indicated in severe acne with extensive secondary lesions.
d. *Other agents* of some benefit in severe cases include- Anti-androgens (cyproterone acetate with ethinyl estadiol) in post-menopausal females *or* Oral isotretinoin-a retinoic acid derivative (0.5–1.0 mg/kg/d for 3–4 months).
e. *Surgical intervention* with aspiration and intralesional instillation of steroids may be necessary in painful nodulocystic lesions. *Dermoabrasion* to minimize scarring is indicated only after active phase is over, beyond the adolescence.

D/D: Other common causes of acne in childhood include:

a. *Drugs*, e.g. steroids, INH, phenytoin, phenobarbitone, iodine compounds (halogen acne),
b. *Transient neonatal acne*, due to placental transfer of androgens, and
c. *Tropical acne*, due to intense hot and humid climate.

25.11.3 SWEAT GLAND DISORDERS

Sweat glands include two types of exocrine glands- apocrine glands and eccrine glands.

Eccrine glands, distributed all over skin including palm and soles, are prime regulators of body temperature. These glands, located in dermis or subcutis, produce sweat that is secreted over skin surface via sweat pores.

Apocrine glands are mainly located in axilla, areola, anogenital area and periumbilical region and continuously secrete an odorless milky fluid (apocrine sweat) during and after puberty. Bacterial decomposition of apocrine sweat is responsible for unpleasant odor of perspiration.

Miliaria rubra and M. crystallina is the commonest disorder of sweat glands due to a occlusion of their ducts by a keratin plug, discussed in Chapter 25.5.

Anhidrosis *or* Hypohidrosis, i.e. absent or less sweating over all or part of the skin may be due to:

a. *Neural pathway disturbances*, e.g. hypothalamic tumors, brain-stem lesions, spinal lesions (syringomyelia), peripheral neuropathies (leprosy), autonomic disorders (Riley-Day syndrome); or
b. *Sweat gland abnormalities*, e.g. congenital absence (ectodermal dysplasia), atrophy or destruction (burns, radiotherapy), drug-induced paralysis (atropine, scopolamine), blocked sweat ducts (miliaria, ichthyosis, atopic eczema).

Severe anhidrosis alters thermoregulatory mechanisms and may present with hyperthermia. Absence of sweating is a diagnostic feature of heat stroke and distinguishes it from heat exhaustion. Hypohidrosis is common in severe dehydration. Sweating is minimal in early infancy.

Hyperhidrosis, i.e. *excessive sweating* may be due to high environmental temperature, exercise or emotional disturbances, though pathological causes include: (a) neurological disorders, e.g. Riley-Day syndrome or spinal cord injuries, (b) metabolic states, e.g. hypoglycemia, hyperthyroidism, rickets, (c) drugs, e.g. antipyretics, insulin, (d) congestive cardiac failure.

Bromhidrosis, i.e. *excessive odor of sweat*, is a common problem in adolescence, due to formation of short-chain

fatty acids and ammonia by action of anaerobic diphtheroids on axillary apocrine sweat. Cleaning with a germicidal soap and topical application of aluminum/zinc containing powders is often enough in most cases.

25.11.4 NAIL DISORDERS

Nails are specialized cuticular structures, consisting of nail plate bounded by lateral and posterior nail folds, covering a crescentic white area (*Lunula*) and underlying vascular bed (giving pink color to nails). Nail abnormalities may be primary or acquired after trauma, infection or chronic systemic diseases **(Table 25.13)**.

Acute paronychia, i.e. *infection of nail bed* is usually caused by staphylococci or streptococci, and presents with inflammation and severe pain/tenderness of proximal nail bed **(Fig. 25.18A)**. Treatment includes oral antibiotics, e.g. amoxicillin/clavulanate, warm compresses, anti-inflammatory agents and incision/drainage in some cases.

Chronic paronychia is more common in children with: (a) finger/thumb sucking, (b) embedded foreign body, e.g. wood splinter, (c) nail trauma, (d) chronic submersion of nails in irritating solutions, (child labor), and (e) diabetes.

TABLE 25.13: Common nail abnormalities

Nail abnormality	*Cause*
Deformity:	
Anonychia (absent nails)	Traumatic, congenital
Platynychia/Koilonychia	Iron deficiency anemia, hereditary, developmental*
Clubbing	*See* Chapter 17.2
Hypoplastic nails	Nail-patella syndrome
Onycholysis (destruction)	Trauma—nail biting Infection—onchomycosis
Periungual fibroma	Tuberous sclerosis
Discoloration:	
Pallor	Anemia
Leukonychia (White lines)	PEM, hypoproteinemia Trauma, infection
Yellow	Meconium staining* Yellow-nail syndrome
Black pigmentation	Normal (10–15%) Chronic infection, traumatic
Splinter hemorrhage	Inferior endocarditis, trauma, Chronic liver disease

*in infants

Fig. 25.18: (A) Acute paronychia; (B) Paronychia.

Microbially, it is often caused by candida or mixed bacterial flora and presents with persistent swelling of proximal nail fold, separation of nail plate and suppuration **(Fig. 25.18B)**. Management includes keeping the nails dry and prolonged topical antibiotic/antifungal therapy.

In-grown nails, i.e. penetration of lateral nail fold/or spicule into surrounding soft tissue may lead to recurrent paronychia and usually seen in cases with poor-fitted footwear and improperly cut nails. Management includes: (a) treatment of local paronychia, (b) cauterization of soft granulation tissue over lateral nail bed, and (c) nail removal in recurrent cases. Nail should be allowed to grow beyond free edge before cutting transversely rather than in curvilinear fashion.

Nail-patella syndrome is an autosomal dominant disorder, characterized by *hypoplastic nail/s and patella (knee instability)* with/without cutis laxa, hyperextensible joints, hyperhidrosis and renal anomalies.

Yellow-nail syndrome (thickened, excessively curved, yellowish nails, without lunula) is seen in bronchiectesis and chronic lymphatic limb edema, e.g. filariasis.

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CHAPTER

26

Ophthalmic Disorders

Mukesh Agrawal

Ophthalmic examination is an integral part of general clinical evaluation, not only to identify local disease but also to suspect or detect many systemic abnormalities. Eye is also considered as a window to visualize intracranial pathology.

26.1 GENERAL CONSIDERATIONS

Anatomical development of eye is near complete at birth, with its size being ~65% of adult size. However, some development immaturities are common even in term newborns and young infants **(Table 26.1)** and should be considered during interpretation of ophthalmic findings in this age-group. In addition, transient corneal haze, hyaloid vascular remnants on posterior lens capsule or optic disc, and retinal hemorrhages are common in preterms, which disappear with maturity.

While periodic ophthalmic screening is indicated in all children for early diagnosis of: (a) developmental or acquired ocular abnormalities, (b) visual/refractory errors, and (c) disorders of ocular motility, e.g. strabismus; all of whom may hamper development of binocular vision with potential risk of amblyopia in developing eye. However, **Table 26.2** enumerates high-risk cases, who need comprehensive and more frequent ophthalmic assessment by experts.

TABLE 26.1: Developmental ophthalmic immaturities at birth

Anatomical
- Thin, translucent, bluish sclera
- Relatively large cornea
- Shallow anterior chamber
- Lightly pigmented iris
- More spherical lens, with *Mitternorf dots**
- Pale retina with peppery/mottled pigmentation
- Relatively pale optic disc
- Immature macula (weak foveal light reflex)

Physiological
- Physiological photophobia
- Low visual acuity (~ 6/120 at birth)
- Physiological hypermetropia till 6–7 years
- Physiological strabismus till 3–6 months

* remnants of fetal hyaloid system

TABLE 26.2: Specific indications for ophthalmic assessment

High-risk cases
- Prematurity
- Perinatal complications/ prolonged NICU stay
- *Systemic diseases:* Diabetes, hypertension, JIA
- Prolonged steroid therapy
- Family history of ophthalmic disease

Clinical indicators
- Delayed visual milestones
- Craniofacial dysmorphism
- Chromosomal/genetic disorders
- *Ocular abnormalities:* Cataract, glaucoma, retinopathies
- *Abnormal eye movements:* Nystagmus, strabismus

Poor school performance

26.2 OCULAR DISORDERS

26.2.1 DISORDERS OF ORBIT

Exophthlamos (proptosis) denotes abnormal protrusion of eye ball, due to: (a) shallow orbit, as in craniofacial malformations, (b) increased orbital mass, e.g. ocular inflammations and tumors, or (c) posterior push on eye ball, e.g. thyrotoxicosis or cavernous sinus thrombosis.

Precise severity of proptosis may be measured by exophthalmometer, as distance between lateral orbital rim to apex of cornea. An absolute value of >20 mm or >2 mm difference between two sides as abnormal. Apart from causative pathology, exophthalmos *per se* may lead to exposure keratoconjunctivitis and refractive errors due to deformed ocular shape.

Enophthalmos is usually secondary to orbital fracture or post-inflammatory atrophy of orbital tissue, presenting as posterior sinking of eye. It should be differentiated from congenital *micropthalmia,* which is common in intrauterine infections.

Orbital cellulitis, i.e. *inflammation of orbital tissue* may develop due to: (a) direct orbital infection, e.g. trauma, (b) as part of generalized septicemia, or (c) extension of infection from neighbouring tissues, e.g. sinusitis (commonest cause in children). Common causative organisms in children are *Staph. aureus, H. Influenza* and anaerobic organisms.

Clinically, it presents with: (a) proptosis, (b) restricted eye movements, (c) chemosis and/or lid swelling, with or without pain.

Prompt therapy with systemic antibiotics and surgical drainage of abscess, if present, is essential to prevent secondary complications, i.e. intracranial extension with cavernous sinus thrombosis, meningitis or brain abscess.

26.2.2 DISORDERS OF EYELIDS

Ptosis, i.e. *drooping of upper eyelids with narrowed palpebral fissure,* may be congenital or acquired.

Normally, upper eyelid covers ~ 2 mm of cornea below the upper limbus.

Congenital ptosis is usually unilateral, due to dystrophy of *levator palpebrae superioris* or rarely, third cranial nerve palsy.

Acquired ptosis may be *bilateral* in neuromuscular disorders, e.g. myasthenia gravis, muscular dystrophy, Horner syndrome (with miosis and anhidrosis), III nerve involvement in CNS disorders; *or unilateral* due to local pressure from a lid mass, e.g. lid hemangioma or plexiform neurofibromatosis. *Marcus Gunn jaw-winking syndrome* is a rare but interesting cause of ptosis, which presents with blinking movements during chewing or sucking due to abnormal synkinesis between 3rd and 5th cranial nerve.

Apart from a cosmetic deformity, long-standing ptosis in visually immature young children may lead to: (a) *amblyopia* due to partial obliteration of visual axis, (b) *astigmatism* due to distortion of eye globe by lid pressure, and (c) *strabismus* due to deprivation amblyopia. In severe cases, child tends to maintain a typical *chin-up head posture* to maintain binocular vision.

Lagophthalmos or lid retraction denotes *difficulty or inability to close the lids* completely over eye-globe, which may be: (a) *physiological,* e.g. during sleep, (b) *structural,* due to post-traumatic/inflammatory lid scarring or in collodion babies, (c) *paralytic,* e.g. facial palsy, (d) *spastic,* e.g. thyrotoxicosis, or (e) *secondary* due to proptosis and buphthalmos. Prolonged lagophthalmos may lead to corneal xerosis, infection and ulceration, which may be prevented by use of artificial tear-drops or tarsorrhaphy in severe cases.

Ectropion, i.e. *eversion of lid margin*, is usually due to post-inflammatory scarring of lids, but may be congenital or associated with facial palsy, due to weight of flaccid lower eyelids. Apart from cosmetic defect, it may lead to exposure keratoconjunctivitis, epiphora and consequent periocular maceration of skin; and hence to be treated surgically.

Entropion, i.e. *inversion of lid margin*, is more troublesome defect, due to associated *in turning* of eyelashes (*Trichiasis*). It is almost always caused by post-inflammatory scarring of lids, e.g. in trachoma and ocular injuries.

Clinically, it presents with constant foreign body sensation due to in-turned eyelashes (*Trichiasis*), leading to frequent rubbing, recurrent ocular infections and corneal abrasions/ulcers; and hence to be treated surgically as early as possible. The term *Epiblepharon* denotes in-turned eyelashes *without* inversion of eyelids.

Blepharitis, i.e. acute, chronic or recurrent *inflammation of eyelids,* presents with erythema and itching of eyelids, with ulceration/scaling in severe cases.

Acute blepharitis is usually a Staph. aureus *or* epidermidis infection, frequently progressing to cause hordeolum (*Stye*), conjunctivitis or keratitis. Treatment involves regular removal of crusts with hot-moist compresses and topical antibiotics with/without steroids.

Chronic/recurrent blepharitis is usually seborrheic in origin, with greasy scales and scalp seborrhea. Regular lid cleaning as above, along with scalp care using selenium sulfide solution is necessary. Blepharitis due to *lice* infestation (Phthiriasis) may need mechanical removal of nits along with topical application of 20% fluorescein with/without systemic Ivermectin therapy in resistant cases.

Hordeolum internum or externum (Stye) are localized *staphylococcal infections* of *Meibomian or Zeis glands* respectively, which present as acute, tender and focal swelling over inner *or* outer margins of eyelids respectively. Stye tends to be more superficial and small. Treatment includes frequent warm compresses and topical antibiotics, with/without surgical drainage. Rare cases may progress to cause orbital cellulitis.

Chalazion is a *non-tender, relatively chronic, nodular swelling of lid* (d/d acute and tender hordeolum) due to granulomatous inflammation of *Meibomian gland,* which may subside spontaneously. Chronic or severe cases needs to be excised for cosmetic purpose and to prevent secondary astigmatism due to pressure on the eye-globe.

Blepharospasm, i.e. *spastic or repetitive closure of eyelids* is normal in newborns due to physiological photophobia, but may indicate underlying ocular infection, foreign body, uncorrected refractory error, or occasionally a habit tic in older children.

Congenital lid anomalies include:

Lid coloboma, i.e. cleft-like lid deformity of variable size is rare congenital abnormality, which may be isolated or associated with other facial malformations, e.g. *Treacher Collins syndrome* and *Goldenhar syndrome*.

Epicanthic folds, i.e. *vertical or oblique folds of skin covering inner canthii* are normal in some races and in newborns (disappear with age), but may also indicate chromosomal defects, e.g. *Down syndrome.*

Oblique or slanting palpebral fissure, i.e. *Mongoloid slant* (outer canthus at a higher level than inner canthus) or *anti-mongoloid slant* (inner canthus higher than outer canthus) may be normal, though more commonly seen in chromosomal disorders, e.g. *Down syndrome.*

26.2.3 DISORDERS OF LACRIMAL SYSTEM

Tears are regular formed in lacrimal and accessory lacrimal glands, located under upper lid at lateral canthus. After formation, these tears bathe the conjunctiva to prevent drying and drain via punctual openings at medial canthus to *nasolacrimal duct* (NLD) into the nose. At birth, lacrimal glands are under-developed with little tear production during first 2–3 months of life.

Tear-film is actually a three-layer structure with—(a) inner-most *mucin layer* from goblet cells of conjunctiva, which fixes the tear-film to conjunctiva/cornea, (b) middle *aqueous layer* of tears from lacrimal glands, and (c) outer *lipid layer* from meibomian gland, to retard evaporation of tears. *Epiphora* (tear-overflow) usually indicates lacrimal gland disorder, while *Alacrima* (dry eye) is usually due to disorders of other tear layers.

Congenital Dacryostenosis (NLD obstruction) is commonest congenital eye problem, present in ~5% newborns due to incomplete canalization of NLD as it enters the nose (*valve of Hasner*).

Clinically, it manifests soon after birth with persistent epiphora, mucoid discharge due to lacrimal sac reflux, secondary infection (dacryocystitis) and periocular maceration of skin.

Management of uncomplicated cases includes—(a) frequent massage over the side of nose to clear the duct, (b) daily cleaning of eyelids with lukewarm water, and (c) topical antibiotics if discharge is mucopurulent. Most cases (>95%) resolve spontaneously by 6–12 months of age. Some may require repeated *punctal probing* or, very rarely, *dacryocystorhinostomy*.

Lacrimal mucocele is a bluish subcutaneous mass just below the medial canthus due to NLD blockade at both, nasal and punctual end, which is managed on similar lines with massage and probing.

Dacryoadenitis, i.e. *inflammation of lacrimal gland*, is uncommon in children. *Acute dacryoadenitis* may occur in viral (mumps, influenza, infectious mononucleosis) or staphylococcal infections; while *chronic dacryoadenitis* is associated with syphilis, tuberculosis and sarcoidosis.

Mikulicz syndrome is a rare disorder, associated with simultaneous enlargement of lacrimal and salivary glands.

Dry-eye (Alacrima), i.e. *absence or deficiency of tears,* indicates congenital or acquired defect in any one or more of the three layers of tear film. Important causes of complete or partial dry eye are—(a) vitamin A deficiency, (b) ocular injury in chronic infections, burns, irradiation, (c) Stevens-Johnson syndrome, (d) familial dysautonomia (Riley-day syndrome), (e) Sjögren syndrome, and (f) anhidrotic ectodermal dysplasia. Apart from the correction of underlying problem, treatment includes frequent instillation of artificial teardrops, occlusion of lacrimal puncta or occasionally, *tarsorrhaphy*.

26.2.4 CONJUNCTIVAL DISORDERS

Apart from primary lesions, conjunctiva being a transparent mucus membrane, is also a window to detect underlying scleral or vascular abnormalities.

Acute conjunctivitis may be infective *or* non-infective in origin **(Table 26.3)**, characterized by conjunctival hyperemia, edema, exudation and ocular discomfort or pain. Some important types of conjunctivitis are discussed below:

Neonatal conjunctivitis *(Ophthalmia neonatorum)* is a potentially blinding condition in newborns, caused by organisms from maternal birth canal, e.g. *N. gonorrhoeae* or *C. trachomatis*, or hospital flora, e.g. Pseudomonas or Staphylococci (Nosocomial).

Gonococcal conjunctivitis usually presents at birth or within first 5 days of life, while *Chalmydia conjunctivitis* typically develops after 5–7th day. Severity of disease may vary from superficial conjunctivitis to secondary complications, e.g. keratitis, iridocyclitis and panophthalmitis.

Early diagnosis by direct gram staining and culture of the discharge as well as microscopic examination of epithelial cell scrapping from tarsal conjunctiva (for chlamydial inclusion bodies) is essential for rational antibiotic therapy.

While regular eye wash with warm saline and topical antibiotics are enough for very mild and non-gonococcal conjunctivitis, other cases need systemic antibiotic therapy with ceftriaxone (gonococci), erythromycin (chlamydia), aminoglycoside (pseudomonas) and cloxacillin (staphylococci).

TABLE 26.3: Common causes of conjunctivitis

- Ophthalamia neonatorum
- *Infections:*
  - *Bact: Staph. aureus, H. influenzae, S. pneumoniae*
  - *Viral:* Adenovirus, Enterovirus, Measles
- *Allergic:*
  - *Exogenous allergens:* Seasonal, vernal
  - *Endogenous allergens:* Phlyctenules
- *Immunological:* Reiter's disease*
- *Chemical:* Topical eye drops, smoke, sprays
- *Others:* Stevens-Johnson syndrome

* with arthritis and urethritis

Crede's method, i.e. topical instillation of 1% silver nitrate at birth has virtually eliminated gonococcal conjunctivitis, though not practiced currently due to low incidence of disease and potential risk of chemical conjunctivitis.

Bacterial conjunctivitis in post-neonatal period is usually caused by *S. aureus*, non-typeable *H. influenzae*, and *S. pneumoniae*.

Unlike viral conjunctivitis, it is usually sporadic and typically purulent. Most cases are preceded by other ocular pathologies, e.g. trachoma, viral conjunctivitis, eye injuries, etc, with superadded bacterial infection. Staphylococcal conjunctivitis may also present as phlyctenular conjunctivitis, discussed later.

Post-neonatal bacterial conjunctivitis usually responds well to warm saline washes and topical antibiotics and systemic antibiotics are rarely required.

Viral conjunctivitis, is the commonest cause of conjunctivitis in children at present, typically presenting as localized seasonal outbreaks, specially in summer season.

Etiologically, most of these outbreaks are caused by changing strains of *adenoviruses* or *enteroviruses*.

Clinically, these cases present with watery discharge, marked hyperemia/chemosis and disproportionately less ocular discomfort. Adenoviral infections are frequently associated with follicles over palpebral conjunctiva, while enteroviral conjunctivitis is often hemorrhagic.

Diagnosis is largely clinical, based on epidemiological profile though conjunctival swabs may be collected in cases with suspicious superadded bacterial infection.

Management: While most cases recover spontaneously in 2–3 days, local pain and inflammation may be minimized with warm saline washes and topical steroids. Topical antibiotics are indicated only in cases with suspected bacterial superinfection.

Epidemic keratoconjunctivitis is an uncommon but special form of viral conjunctivitis due to *adenovirus type 8*, characterized by large oval follicles and/or pseudomembrane formation, along with acute pharyngitis and pre-auricular adenopathy.

Allergic conjunctivitis is characterized by typical seasonal pattern, similar family history, presence of eosinophils in discharge and excellent response to topical steroids. Presence of *chemosis,* i.e. severe swelling of conjunctiva without significant hyperaemia strongly indicates allergic angioneurotic edema.

Vernal conjunctivitis is a typical form of allergic conjunctivitis with *cobble-stone* papillary lesions over palpabral conjunctiva, more common in adolescents.

Phlyctenular keratoconjunctivitis is an interstitial conjunctivitis, considered as a *delayed hypersensitivity* response to endogenous antigens, e.g. tuberculosis, staphylococci and parasitic antigens.

Phlycten is a tiny pinkish-yellow nodule or bleb usually at the limbus, which may encroach over cornea and expand centrally. A small fascicular ulcer is often present over the head of advancing lesion. Most cases recover spontaneously in 5–7 days.

No specific treatment is required in asymptomatic cases, though topical steroids may be used to reduce inflammation, along with topical antibiotics (in suspected bacterial infection) or atropine drops (if cornea is involved). Anti-tubercular therapy is not indicated as a routine, but active tuberculosis should be excluded by chest skiagram and tuberculin test.

Chemical conjunctivitis may develop after exposure to topical drugs, e.g. silver nitrate, sprays and accidental splash of chemicals. Prompt management with copious eye-wash and topical antibiotics to prevent super-added infection is essential to prevent secondary scarring.

Red-eye is the commonest clinical presentation of many ocular infections, e.g.: (a) conjunctivitis, (b) keratitis, (c) iridocyclitis, (d) acute blepharitis or orbital cellulitis; and non-infective inflammations, e.g. (e) foreign body or other ocular trauma, and (f) eye-strain in severe refractive errors. Important differentiating features of three common ocular infections with red-eye are given in **Table 26.4**.

Trachoma is the one of the commonest cause of preventable blindness in Indian children, caused by *Chlamydia trachomatis*. Infection is more prevalent in poor hygienic and overcrowded living conditions, acquired via hand-to-hand contact or flies.

Clinically, early acute stage presents in as follicular conjunctivitis, which gradually progresses into chronic ocular disease with persistent conjunctival follicles, cicatrisation, scarring and secondary deformities, e.g. entropion and corneal opacities.

Diagnosis is largely clinical, based on following *WHO criteria*: (a) lymphoid follicles on upper tarsal conjunctiva, (b) conjunctival scarring, (c) vascular pannus, and (d) limbal follicles. It may be confirmed in acute stage by direct staining and culture.

TABLE 26.4: D/D of Red-eye in children

	Conjunctivitis	***Keratitis***	***Iridocyclitis***
Main cause	Infection	Trauma	Immune
Congestion	Conjuctival	Ciliary	Ciliary
Vision	N	-	-
Photophobia	+	++	++
Discharge	++	++	+
Pupils	N	Constricted	Constricted
Treatment	Ab	Ab + C	C + Steroids

Ab: Antibiotics; **C:** Cycloplegic agents, e.g. atropine

Management involves eradication of infection by prolonged use of topical antibiotics (Tetracycline/Erythromycin) with/without a short course of oral antibiotics (Azithromycin 3 days) and correction of secondary deformities.

Symblepharon is a *cicatricial adhesion between palpebral conjunctiva and the eye-globe*, following infection, injury, e.g. chemical burns/surgery, *or* other inflammatory disorders, e.g. Stevens-Johnson syndrome. It may cause diplopia by restricting ocular movements and adhesions need to be separated surgically, followed by mucosal graft, if necessary.

Subconjunctival hemorrhages may be spontaneous or secondary to trauma, infection, severe cough, (e.g. pertussis) or blood dyscrasia, e.g. thrombocytopenia. As the blood is usually reabsorbed spontaneously in 4–6 weeks, no intervention is required in most cases except exclusion of more severe ocular lesions and primary pathology.

Vitamin A deficiency is associated with various conjunctival lesions, e.g. ***Xerosis,*** i.e. dry, wrinkled, lusterless or muddy conjunctiva due to cornified epithelium, not limited to interpalpabral region (d/d exposure conjunctivitis/muddy sclera) and ***Bitot's spots,*** i.e. chalky-gray triangular plaques due to heaped-up dry epithelium, usually over temporal conjunctiva. These lesions persist for long time even after recovery from the deficiency state. Corneal and retinal involvement should be excluded in severe cases (Ch 6.2).

Pinguecula is an idiopathic, yellowish-white, *focal degenerative lesion* of bulbar conjunctiva, usually in interpalpebral region. These lesions are more common in *Gaucher disease*. No treatment is needed except excision, if cosmetically warranted.

Pterygium is an *idiopathic degenerative lesion* of conjunctiva, presenting as fleshy triangular lesion over nasal interpalpabral region, which may encroach upon cornea. It is sometimes considered as related to the exposure to ultraviolet light. No treatment is required except cosmetic excision. Recurrence is common.

26.2.5 SCLERAL DISORDERS

Episcleritis is a benign and frequently recurrent disorder in adolescents and young adults, presenting with *raised congested nodules near the limbus,* rarely associated with other signs of inflammation. It is usually considered as a *hypersensitivity reaction* to variety of antigens, e.g. tuberculosis or syphilis, or associated with autoimmune rheumatic disorders. Recovery is spontaneous in 2–3 weeks, though topical steroids may be used in symptomatic cases.

Scleritis is more acute and severe inflammation of sclera, rare in children. It is a rapidly progressive inflammation with severe pain and scleral thinning, occasionally seen in rheumatoid disorders, e.g. juvenile rheumatoid arthritis and SLE.

Scleral discoloration is an important guide for many systemic disorders, e.g. icterus (yellow), cyanosis (bluish-hue vascularity), alkaptonuria (black), etc.

Blue sclera indicates relatively thin sclera, due to: (a) developmental immaturity in normal newborns and infants), (b) collagen disorders, e.g. osteogenesis imperfecta, Ehler-Danlos syndrome, etc. and (c) excessive stretching, e.g. Buphthalmos and high myopia.

26.2.6 CORNEAL DISORDERS

Congenital abnormalities of cornea, include:

Megalocornea, i.e. *a corneal size of >12 mm*, may be an isolated defect *or* associated with Marfan syndrome, craniosynostosis and osteogenesis imperfecta. Acquired increase in corneal size, i.e. *Buphthalmos*, is seen in congenital or infantile-onset glaucoma, due to increased ocular pressure and stretching of immature cornea.

Microcornea, i.e. *a corneal size of <6 mm* or smaller than opposite side, is an indicator of intrauterine infections, e.g. congenital rubella syndrome or chromosomal disorders, though some cases may be familial. It is rarely an isolated defect, often associated with microphthalmia, cataracts and retinal abnormalities.

Keratoconus, i.e. *cone-shaped cornea with central thinning* may be post-traumatic or associated with congenital anomalies, e.g. Down syndrome, Marfan syndrome and osteogenesis imperfecta. High myopia is common in these cases, due to increased anteriorposterior distance of visual axis.

Keratitis/corneal ulcer is a potential vision-threatening inflammation of cornea, more common and often recurrent in children with: (a) pre-existing corneal pathology, e.g. vitamin A deficiency, (b) reduced corneal sensations, e.g. Riley-Day syndrome, and (c) prolonged eye-exposure, e.g. proptosis.

Etiologically, foreign body injuries are commonest cause of keratitis in children, followed by spread from other ocular infections and vitamin A deficiency **(Table 26.5)**.

TABLE 26.5: Causes of keratitis/corneal ulcer

1. ***Ocular trauma*** with/without secondary infection
2. ***Nutritional:*** Vitamin A deficiency
3. ***Local infections:*** Conjunctivitis, orbital cellulitis
4. ***Systemic infections:***
   Viral : Measles, HSV (Dendritic ulcer), VCZ
   Bacterial : Tuberculosis (Phylectenules)
   Spirochetal : Syphilis
5. ***Developmental*** corneal defects/degenerations

TABLE 26.6: Causes of corneal opacities

Acquired
- Vitamin A deficiency
- *Traumatic:* Ocular injuries, exposure keratopathy
- *Inflammatory:* Infective keratitis
- Glaucoma

Congenital *(or since early life)*
- Intrauterine infections, e.g. congenital rubella
- Perinatal eye injury (birth trauma)
- Inborn errors of metabolism, e.g. MPS, GSDs
- *Others:* Sclerocornea, hereditary keratopathies

MPS: Mucopolysaccharoidosis; **GSD:** Glycogen storage disorders.

Clinically, these cases present with photophobia, epiphora, ocular pain, circumciliary congestion and focal/diffuse corneal haze.

Diagnosis is based on slit-lamp visualization of lesion, before and after fluorescein staining *and* microbiological studies on corneal scrapping.

Management includes intensive topical therapy with antimicrobials and cycloplegic agents (to prevent synechiae formation), systemic antibiotics and surgical debridement in non-healing cases. Drug of choice for dendritic corneal ulcers due to HSV infection is topical 5-iodo-2-deoxyuridine (IDU).

Complications of keratitis/corneal ulcers include: (a) hypopyon, i.e. pus in anterior chamber, (b) corneal perforation and opacities, (c) posterior synechiae with secondary glaucoma, and (d) spread of infection to deeper structures, e.g. uveitis or panophthalmitis.

Corneal opacities may be congenital or acquired and focal *or* diffuse. In Indian children, Vitamin A deficiency and corneal injuries are two most common causes of corneal opacities **(Table 26.6)**.

Sclerocornea is an important cause of congenital and familial corneal opacity, characterized by replacement of transparent cornea by a sclera-like tissue, specially in peripheries. Except sclerocornea and congenital rubella, other congenital keratopathies usually do not manifest at birth and develop over a period of time.

Prompt detection and treatment (keratoplasty, corneal transplant) is essential in childhood corneal opacities, to prevent development of amblyopia.

Corneal pigmentation usually indicate a metabolic disorder, e.g. presence of *Kayser-Fleischer ring* a golden-brown ring near the limbus in Wilson disease, *refractile crystals* in cystinosis and *golden-brown deposits* in alkaptonuria.

26.2.7 UVEAL TRACT DISORDERS

Uveal tract, the inner vascular coat of eye, includes three structures—iris, ciliary body and choroids. ***Uveitis,*** i.e. inflammatory disorders of uveal tract may be infective or non-infective in origin **(Table 26.7)** and include anterior uveitis (*Iridocyclitis*), posterior uveitis (*Chorioretinitis*), panopthalmitis and sympathetic ophthalmitis.

TABLE 26.7: Common causes of uveitis

Anterior uveitis (iridocyclitis)
- *Infections:* Viruses, e.g. HSV, VCZ, syphilis
- *Trauma:* Foreign body, blunt/penetrating injury
- *Autoimmune:* Rheumatoid arthritis, Kawasaki disease
- *Others:* Drugs, Stevens-Johnson syndrome
- Idiopathic

Posterior uveitis (choroidoretinitis)
- Intrauterine (TORCH) infections
- Postnatal infections, e.g.
  - *Viral* : HSV, HIV, CMV, Rubella
  - *Granulomatous* : TB, Brucellosis, sarcoidosis
  - *Parasitic* : Toxoplasmosis
- Idiopathic

Panophthalmitis
- Septicemia
- Penetrating eye injuries

Sympathetic ophthalmitis
- Reactive (injury to other eye)

Acute iridocyclitis is usually infective in origin **(Table 26.7)** and presents with intense eye pain, lacrimation, photophobia. Important ocular signs include circumciliary congestion, *aqueous flare* (proteins/cells in anterior chamber), *keratic precipitates* (kp) on posterior surface of cornea, muddy iris and small, irregular, sluggishly reactive pupil.

Prompt diagnosis and therapy with systemic antibiotics, intra-ocular antibiotics (in some cases) and topical cycloplegic agents are necessary to prevent complications like: (a) synechiae formation with glaucoma, (b) corneal degeneration, e.g. band keratopathy, (c) lenticular opacities, and (d) impairment of vision.

Chronic iridocyclitis is usually seen in autoimmune rheumatoid disorders, e.g. JRA, SLE, etc. and may be entirely asymptomatic till visual loss. Systemic steroids or immunosuppressive therapy is necessary to prevent and treat these cases.

Chorioretinitis is often chronic and asymptomatic, till diagnosed on routine ophthalmic examination or development of secondary complications. Intrauterine infections are most common cause of chorioretinitis in children, though ocular finding may not be present at birth and appear at a later age.

Chorioretinitis in CMV is typically diffuse except at macula, while macular involvement is characteristic of congenital toxoplasmosis. Complications of posterior uveitis include retinal detachment, glaucoma and phthisis

Panophthalmitis is an acute suppurative condition involving nearly all ocular tissues, usually after perforating eye injury or septicemia. It is an ocular emergency, presenting with intense pain, inflammation and visual loss. Intensive antibiotic therapy *with* enucleation or evisceration of orbit is necessary to

prevent sympathetic ophthalmitis and loss of vision in other eye.

Sympathetic ophthalmitis affects the normal eye after many weeks/years of the injury to one eye and considered as a *hypersensitivity* phenomenon. Loss of vision in uninjured eye develops rapidly, which may be prevented by enucleation of injured eye before the development of sympathetic ophthalmitis.

Developmental disorders of uveal tract mainly involve the iris and include:

Aniridia, i.e. congenital absence/hypoplasia of iris, is almost always bilateral. Although most of these cases are familial, sporadic aniridia is of main interest due to frequent association with Wilms tumor, urogenital abnormalities and mental retardation. Other ocular defects, e.g. glaucoma, cataracts and macular or optic nerve hypoplasia are common in these cases.

Coloboma of iris is a development defect, usually located inferiorly (*key-hole iris*). Although it is unlikely to affect vision, these cases should be investigated for other ocular abnormalities.

Heterochromia *iridum* (different colors of two iris) or *H. iridis* (different colors in same iris) may be an isolated familial condition *or* associated with *Waardenburg syndrome,* i.e. partial albinism with white forelock, deafness and heterochormia. Pink iris is seen in albinism and blue in partial albinism.

Other iris abnormalities include ***Lisch nodules,*** i.e. discrete nodules over iris in neurofibromatosis and ***Brush-field spots,*** i.e. sand-grain like deposits in Down syndrome.

26.2.8 PUPILLARY DISORDERS

Normally pupil is ~3–4 mm in size at room light and light reflex is present from 31st week of gestation.

Examination of pupillary size, symmetry and reactivity to light is of immense value in diagnosis of neurological disorders, poisonings and retinal disease **(Table 26.8)**.

Dyscoria or corectopia, i.e. abnormal shape or location of pupil is secondary to iris deformities, which may congenital or acquired after ocular trauma, uveitis and anterior synechiae formation. Congenital defects are usually associated with ectopia lentis.

Leukocoria, i.e. white pupillary reflex or cat-eye reflex, indicates abnormalities of lens, posterior chamber or retina. It may be developmentally present in preterms due to incomplete regression of fetal hyaloid vascular system, which clears spontaneously in next few weeks. Important causes of pathological leukocoria include—(a) cataract, (b) retinoblastoma, (c) retinopathy of prematurity, (d) retinal detachment, and (e) leukemic infiltrates in eye.

TABLE 26.8: Abnormal pupilary size and reactivity

Constricted, non-reacting pupil *(Fixed miosis)*
- Congenital miosis or microcoria
- *Drugs:* Pilocarpine
- *Poisoning:* Opium, barbiturate, organophosphorus
- Pontine hemorrhage
- Horner syndrome (Miosis, Ptosis, Anhidrosis)

Dilated, non-reacting pupil *(Fixed mydriasis)*
- Cardiopulmonary arrest
- Drugs: Atropine, other cycloplegics
- Transtentorial herniation (Hutchinson's pupil)
- Intracranial hypertension
- Ocular trauma or infections (Tonic pupil)
- Riley-Day syndrome

Anisocoria *(asymmetrical pupils)*
- Congenital coloboma or aniridia
- Unilateral neurological disease
- Post-infective/traumatic synechiae
- Topical drugs, e.g. atropine, pilocarpine

Paradoxical pupil *(abnormal constriction in dark)*
- Night blindness
- Albinism
- Retinal disorders

Marcus Gunn pupil *(Direct LR –ve, consensual LR +ve)*
- Retinal or optic nerve disease

Hippus (Rhythmic dilatation and constriction of pupils)
- Retrobulbar neuritis

LR: Light reflex

26.2.9 GLAUCOMA

Glaucoma, i.e. *raised intraocular pressure,* is an important cause of visual impairment due to secondary pressure effects on optic nerve. Unlike adults, childhood glaucoma is almost always caused by defective drainage of aqueous fluid.

Etiologically, it may be classified as *congenital glaucoma* due to anatomical abnormalities of the trabecular drainage network; and *Secondary glaucoma* due to post-traumatic or post-inflammatory obstructive lesions **(Table 26.9)**. However, even congenital glaucoma may not be evident at birth and develops after many weeks.

TABLE 26.9: Causes of glaucoma in children

Congenital glaucoma (>50%)
- *Intrauterine infections:* Congenital Rubella
- *Chromosomal disorders:* Down syndrome
- *Genetic disorders:* MPS, Homocystinuria
- *Connective tissue defects:* Marfan syndrome
- Neurocutaneous syndromes

Secondary glaucoma
- *Injury:* Trauma to ciliary body
- *Inflammations:* Iridocyclitis
- Intraocular hemorrhage
- Intraocular tumors
- *Iatrogenic:* Prolonged steroid therapy

MPS: Mucopolysaccharoidosis

Other ocular abnormalities, e.g. aniridia, cataracts, spherophakia and ectopia lentis are commonly associated in congenital glaucoma.

Clinically, glaucoma presents with a triad of: (a) epiphora, (b) photophobia, and (c) blepharospasm, with or without vision impairment. Examination may reveal circumciliary congestion (red-eye), corneal edema and/or enlargement (*Buphthalmos*) and raised intraocular pressure on tonometry. Buphthalmos is only seen in congenital glaucoma, when cornea is still stretchable and may lead to breaks in Descemet's membrane (*Haab's striae*) with residual corneal scarring.

Diagnosis rests on tonometry, which may require anesthesia in very young children.

Treatment is surgical in most cases, involving procedures to facilitate aqueous drainage (*goniotomy or trabeculotomy*) and/or to reduce its production (*cyclocryotherapy or photocoagulation*).

Prognosis depends on the cause, severity and damage at the time of diagnosis. Some visual impairment is common in most cases due to corneal scarring, amblyopia and pressure damage to optic disc.

26.2.10 LENS DISORDERS

Lens is a biconvex transparent structure behind the iris and in front of vitreous body, which transmits and permits eye to focus the visual image over the retina.

Cataract, i.e. focal or diffuse opacity of lens in children may be congenital or acquired **(Table 26.10)**. However, congenital cataract may not be apparent at birth and develop after for few weeks or months. Congenital cataracts are one of the most important and consistent indicators of intrauterine infections, especially congenital rubella syndrome. Early detection and surgery is essential in children due to rapid development of deprivation amblyopia.

TABLE 26.10: Causes of cataract in children

Congenital
- *Developmental:* Preterms, vascular remnants[1]
- Familial
- Intrauterine (TORCH) infections
- *Chromosomal:* Trisomies, turner syndrome
- *Genetic:* Galactosemia, lowe syndrome

Acquired
- *Post-traumatic:* Contusion, penetrating injuries
- *Post-infective:* Iridocyclitis
- *Metabolic:* Diabetes, hypoglycemia, hypocalcemia
- *Endocrinal:* Hypoparathyroidism
- *Iatrogenic:* Steroids[2], radiation, hypervitaminosis D

[1]Mittendorf's dots – persistent hyaloid remnants
[2]usually posterior subcapsular

Ectopia lentis, i.e. *displacement or subluxation of lens* from its normal position may be *congenital:* (a) isolated familial defect, (b) marfan syndrome (superiolateral), (c) homocystinuria (inferio-medial), (d) Ehler-Danlos syndrome; or *acquired* after, (e) ocular trauma, (f) ocular diseases, e.g. uveitis or tumors. Most of these cases are asymptomatic, though some may develop blurred vision and refractive errors. *Iridodonesis,* i.e. tremulousness of iris, is an important sign of ectopia lentis along with deep anterior chamber and visible crescentic edge of lens.

26.2.11 RETINAL DISORDERS

Retina is a layer of photoreceptors cells and glial cells lining the posterior segment, which captures incoming photons and transmits them along neuronal pathways as both electrical and chemical signals for the brain to perceive a visual picture.

Retinopathy of prematurity (ROP), earlier termed as Retrolental fibroplasia, is an important retinal disorder, characterized by variable severity of *"arrested or abnormal vascularization of retina"*, almost exclusively seen in preterms.

Pathogenesis: Till 16th week, retina is an avascular structure, when gradual vascularization begins from optic disc toward periphery to reach outer rim of retina (ora serrata) by 36–40th week. Any insult to this process leads to—(a) sudden cessation of vascularization, (b) cellular hypoxia to non-vascularized segment, and (c) release of endothelial growth factors, leading to neovascularization.

This hypoxic tissue injury, coupled with neovascularization, leads to scarring and cicatrisation of retinal tissue, proliferation of extra-retinal fibrovascular tissue and retinal detachment due to vitreous traction.

Risk factors: *Prematurity* (<32 weeks) and *prolonged hyperoxia* due to high concentration oxygen therapy in neonatal period are two most important risk factors for development of ROP, though other contributory factors include hypoxia, infection, acidosis and severe anemia in newborns.

Classification: ROP is variably classified according to the location, extent and severity of disease, though the most common classification is given in **Table 26.11**.

TABLE 26.11: Classification of ROP

Stage	*Ophthalmoscopic findings*
I	Sharp, flat demarcation line separating vascular and avascular retina
II	Pinkish ridge-like growth over this line
III	Presence of extra-retinal fibrovascular tissue
IV a	Subtotal retinal detachment, not involving macula
IV b	Subtotal retinal detachment, involving macula
V	Total retinal detachment

Clinical course: In >90% of infants, ROP arrests spontaneously with no significant residual effect on vision. However, <10% babies progress to develop severe disease, with significant retinal vasoproliferation, cicatrisation, detachment and vision impairment.

Diagnosis depends on follow-up ophthalomoscopy, **(Fig. 26.1A)** which is recommended in all extreme preterms (<32 weeks or 1.5 kg) or more mature newborns with stormy neonatal course, at ~ 6 weeks and then at ~6 months.

Treatment depends on severity and course of disease. Cryosurgery or laser photocoagulation of avascular retina is recommended in progressive and severe cases, to prevent further damage. Vitroretinal surgery to reattach detached retina is so far not very successful.

Prevention of ROP depends on: (a) prevention of prematurity, (b) rational use of oxygen supplementation, and (c) use of antioxidants, e.g. vit E, which is not proven.

Persistent hyperplastic primary vitreous (PHPV) denotes a developmental immaturity with persistence of variable remnants of hyaloid vascular system. Fetal hyaloid artery, which extends from optic disc to the posterior vascular capsule of lens, gradually regresses by 7–8th months. Small remnants of this vascular system may remain attached to the disc (*Bergmeister's papilla*) or lens (*Mittendorf's dots*) in normal children with no vision problem. However, larger remnants are termed as

PHPV, presenting with leukocoria (cat-eye reflex), visual impairment and spontaneous intraocular hemorrhage. Posterior PHPV (attached to the optic disc) may also cause retinal detachment.

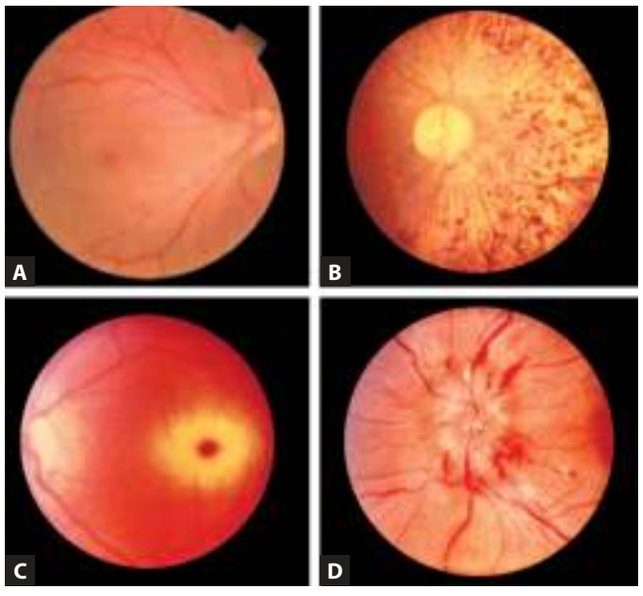

Fig. 26.1: Important fundus abnormalities: (A) Retinopathy of prematurity; (B) Retintis pigmentosa; (C) Cherry-red spot over macula; (D) Papilledema.

Surgical removal of lens with attached tissue is indicated in severe cases, followed by lens implant and correction of refractive error.

Retinitis pigmentosa (RP) is a progressive retinal degenerative disorder, characterized by: (a) abnormal retinal pigmentation, and (b) arteriolar attenuation/narrowing, leading to progressive loss of vision **(Fig. 26.1B)**. Other ocular defects, e.g. cataract, glaucoma, optic atrophy, etc. are common.

Etiologically, Common causes of RP include: (a) intrauterine infections, (b) neurodegenerative disorders, (c) metabolic disorders, e.g. mucopolysaccharidosis, Refsum disease, (d) congenital syndromes, e.g. Laurence-Moon-Biedel syndrome, Leber congenital retinal amaurosis, etc. or (e) drugs, e.g. prolonged chloroquine or phenothiazine therapy.

Clinically, visual impairment begins as night-blindness and progresses gradually to loss of peripheral vision (*Tubular vision*). *Central vision is usually spared*. Electroretinography is typically abnormal in these cases.

Cherry-red spot over macula is an important ophthalmoscopic finding in various neurodegenerative disorders, e.g. sphingolipidoses, gangliosidoses and metachromatic leukodystrophy. It appears as a bright to dull red spot in the center of macula surrounded by a grayish-white or yellowish halo, due to opacification of surrounding retinal ganglion cells **(Fig. 26.1C)**. As fovea does not have ganglion cells, it remains transparent and transmits the red color of underlying vascular choroid (red-spot). Cherry-red spot may also develop in *peripheral retina* (d/d macular lesion) due to retinal ischemia following vascular lesions.

Retinal phakoma are pathognomonic lesions of various neurocutaneous disorders, e.g. Tuberous sclerosis (*mulberry lesion*), Neurofibromatosis, and Sturge-Weber syndrome (*hemangioma*)

Retinal detachment, i.e. separation of outer layer of retina from underlying pigmented epithelium may be: (a) *traumatic,* following retinal injury that allows vitreous fluid to seep into subretinal space, (b) *tractional* due to presence of a vitreoretinal membrane that pulls the retina, e.g. in ROP, sickle cell disease and diabetes, and (c) *exudative* due to collection of exudates in subretinal space in chorioretinitis or retinoblastoma.

These cases present with loss of vision, leukocoria and strabismus/nystagmus. Diagnosis rests on ophthalmoscopy, though orbital CT/MRI imaging is necessary to establish the cause.

Retinal hemorrhage/infarcts, appear as cotton-wool spots on fundoscopy, seen in hypertensive retinopathy, severe anemia, sickle cell disease, leukemia and infective endocarditis (*Roth's spots*—hemorrhages with white center), etc.

Acute hypertensive retinopathy is characterized by: (a) generalized constriction of arterioles, (b) retinal edema, (c) flame-shaped hemorrhages, (d) cotton-wool spots, denoting retinal infarcts, and (e) papilledema. In longstanding cases, thickening of vessels may produce *silver-wire or copper-wire* appearance.

26.2.12 OPTIC NERVE DISORDERS

Papilledema, i.e. *swelling of optic nerve head,* secondary to raised intracranial pressure (ICP), is commonest optic nerve lesion, characterized by:

- Loss of spontaneous venous pulsations (earliest),
- Hyperemia and edematous blurring of disc margins,
- Obliteration *or* fullness of optic disc cup,
- Peri-discal retinal edema, hemorrhages, exudates or concentric retinal wrinkling (*Paton lines*) in severe cases **(Fig. 26.1D)**.

Etiologically, papilledema indicates raised ICP due to cerebral edema, obstructed CSF flow or increased CSF production **(Table 26.12)**. Elevated CSF pressure in subarachnoid space leads to similar pressure-rise within the optic nerve sheath, consequent vascular stasis and nerve edema. Infants with open fontanels and sutures are less likely to develop papilledema due to outward release of CSF pressure. Presence of papilledema has to be excluded before lumber puncture, to avoid risk of sudden brain-stem herniation, i.e. *coning*.

Clinically, these cases present with features of raised ICP, *e.g.* headache, vomiting, bradycardia, hypertension and false localizing signs, e.g. lateral-rectus (VI nerve) palsy. (Ch 18.4) Vision is normal in acute papilledema but may be impaired in late stages due to secondary optic atrophy, macular scarring and pressure damage on optic nerve.

D/D of papilledema includes other causes of similar fundal changes, e.g. acute optic neuritis (vision impaired in early stages), hypertensive retinopathy, diabetic retinopathy and rare *pseudopapilledema*-a structural disc abnormality.

Treatment of papilledema is essentially the treatment of raised ICP (Chapter 18.4). Acute papilledema is completely reversible within 6–8 weeks, if CSF pressure is relieved in initial stages. However, long-standing cases are irreversible due to secondary neurovascular changes.

Optic neuritis, i.e. *"inflammation, demyelination and/or degeneration of optic nerve with loss of vision"* is usually an acute illness in children, which may be unilateral or bilateral. Depending on the portion of nerve affected, it is termed as *Retrobulbar neuritis* (posterior segment), *Papillitis* (nerve-head) or *Neuroretinitis* (associated retinal involvement).

Etiologically, it is seen in: (a) viral nerve-head infections, (b) toxic neuritis, e.g. lead, vincristine, (c) CNS infections, e.g. meningitis, and (d) demyelinating diseases, e.g. multiple sclerosis.

Neuromyelitis optica (Devic disease) is a rare disease with sudden blindness due to bilateral optic neuritis and paraplegia due to transverse myelitis.

Treatment of optic neuritis depends on primary cause. IV or local steroids have been demonstrated to speed-up the recovery in young adults, but do not affect the final outcome. In most cases of primary optic neuritis, recovery begins after 1–4 weeks though complete vision may not be restored.

Optic atrophy, i.e. *irreversible degeneration of optic nerve axons* with attendant loss of vision, is characterized by: (a) disc pallor, and (b) deepening of optic cup on fundoscopy.

Etiologically, it may be *primary*, i.e. without preceding papilledema, due to familial or hereditary degeneration; or more likely *secondary*, following optic neuritis or prolonged papilledema. Disc margins are *well defined in primary* and *obscure in secondary* optic atrophy.

Optic nerve glioma is the commonest but benign tumor of optic nerve, which may develop in intra-orbital or intra-cranial portion of nerve.

Clinically, intra-orbital tumor presents with unilateral blindness and proptosis, while intra-cranial tumor usually involves optic chiasma and manifests with bitemporal hemianopia, raised ICP and hypothalamic/pituitary dysfunction.

As these tumors are very slowly progressive, best therapeutic approach is periodic observation, followed by surgery for intraorbital tumor (if vision is completely lost) *or* radiotherapy/chemotherapy for intracranial tumor.

Congenital abnormalities of optic nerve are rare and include *optic nerve aplasia/hypoplasia*, which is typically unilateral and frequently missed due to normal vision in other eye; and tilted or funnel-shaped (*morning-glory*) disc with significant visual impairment or astigmatism.

TABLE 26.12: Common causes of papilledema

- *CNS infections:* Meningitis, encephalitis
- *ICSOLs:* Brain tumors, tuberculoma
- Head injury
- Intracranial hemorrhage
- *Toxic encephalopathy:* Poisonings, metabolic
- *Developmental:* Hydrocephalus, craniosynostosis

ICSOL: Intracranial space occupying lesions

26.2.13 OCULAR INJURIES

Ocular injuries are one of the commonest causes of blindness in children, accounting for ~1/3rd of all cases. These injuries are more common in adolescent boys (4:1) and often preventable, caused by sport-accidents, foreign body, fire-works and occasionally child-abuse. Although spectrum of ocular injuries is diverse **(Table 26.13)**, important ones are discussed here.

TABLE 26.13: Common eye injuries in children

- Foreign body
- Blunt trauma
  - *External:* Lid injuries, subconjunctival hemorrhage
  - *Deep:* Hyphema, retinal detachment
  - Orbital injuries and fractures
- Penetrating injuries
- Chemical injuries and burns

Foreign bodies are commonest cause of ocular injuries, usually lodged over conjunctiva and cornea and may be floating or embedded.

Sudden development of unilateral red-eye, irritation and epiphora strongly suggests presence of an ocular foreign body, though visualization may be difficult in a struggling child. Conjunctival foreign bodies tend to lodge behind the upper tarsal plate that should always be examined after lid-eversion, while corneal bodies are best seen on slit-lamp examination.

Preliminary management of ocular foreign bodies include gentle removal with a wet cotton bud (if visible and floating) and/or irrigation of eye with plenty of water (if not localized), followed by instillation of antibiotic eye drops. Embedded/occult foreign bodies need ophthalmic referral for removal under slit-lamp. Corneal abrasion/ulceration is the most important complication in these cases, which may be prevented by restraining the child against eye rubbing.

Blunt ocular injuries are often ignored in early stages of head injury and range from self-resolving periorbital or subconjunctival hematoma (*black/red eye*) to serious orbital fractures.

Possibility of orbital fracture should be suspected in a trauma case with—(a) limitation of upward gaze, (b) lower lid ecchymosis, (c) epistaxis, and (d) ipsilateral facial hyperasthesia due to infraorbital nerve injury as it traverses through orbital floor. Even in absence of significant vision impairment, all cases of blunt eye injury should be examined for *hyphema* (blood in anterior chamber) and retinal detachment.

Penetrating eye injuries are less common but more serious, usually associated with injury to multiple ocular structures. *Firework-accidents* are common cause of penetrating eye injuries during festive or wedding seasons in India, usually associated with superficial ocular burns or foreign bodies.

As severe hemorrhage, vision loss and superadded infections are common, these cases should be promptly referred to ophthalmologist after padding the eye.

Chemical eye injuries are usually caused by exposure to domestic or industrial acids *or* alkali, later being more severe due to saponification of eye-fat that allows further penetration of alkali. Corneal involvement and consequent scarring is the major concern in these cases.

Emergency management of chemical ocular burns include—(a) immediate irrigation with water or saline, (b) removal of foreign particles during irrigation, if visible, (c) topical antibiotic instillation, and (d) immediate referral to ophthalmologist.

26.3 VISION DISORDERS

Normal vision depends on normal ocular media, visual axis, image formation over retina, reception over retina, afferent optic nerve and central processing.

Consequently, disorders of vision may be divided into—(a) amaurosis (blindness), (b) amblyopia, i.e. defective central processing, (c) abnormal image formation, i.e. refraction, and (d) abnormal visual axis, i.e. strabismus or other ocular movement disorders. Visual assessment in children needs age-appropriate modifications in vision tests. **Table 26.14** lists common tests, used to assess vision at different ages in childhood.

26.3.1 AMAUROSIS (BLINDNESS)

Amaurosis denotes *severe or complete loss of vision* due to organic causes, which may be primary (congenital) or secondary (acquired) **(Table 26.15)**. Blindness at birth or in early life may be easily missed due to lack of clinical symptoms, difficulties in vision assessment and delayed appearance of objective signs, e.g. fundal changes in hereditary retinopathies.

Perception of light (PL), i.e. blinking or papillary constriction on exposure to torchlight and *Projection of rays* (PR), i.e. movement of gaze or head towards the light source are two commonly used tests to detect blindness in newborn or early infancy.

TABLE 26.14: Assessment of vision in children

Newborn – 6 months
- Pupillary reflex
- Fixing and following light
- Corneal light reflex (for strabismus)

6 months – 3 years
- Reach-out to colored objects
- Preferential looking tests (*Teller* acuty cards)
- Retinoscopy
- Electrophysiological tests:
  - Pattern induced visual evoked response
  - Optokinetic response to a moving object
- Cover test (for strabismus)

3 years – 5 years
- Picture tests and matching cards (*Kays* symbols)
- Tumbling E or HOTV cards
- Cover test (for strabismus)

Above 6 years (Conventional tests)
- *Snellen's* chart (alphabet, tumbling E, landolts-C)
- Visual field assessment
- Color-vision test

TABLE 26.15: Causes of blindness in children

Congenital (primary) blindness
- ***Congenital ocular defects***
  - Congenital cataract
  - Congenital glaucoma
  - *Retinal defects:* Leber congenital retinal amaurosis
  - Optic nerve aplasia/hypoplasia or coloboma
  - *Others:* Corneal opacities, microphthalmia
- ***Congenital CNS malformations***
  - Porencephaly, hydranencephaly, encephalocele
- ***Intranatal/perinatal injuries***
  - Intrauterine (TORCH) infections
  - Birth asphyxia
  - Birth trauma

Acquired (secondary) blindness
- ***Ocular defects***
  - Vitamin A deficiency
  - *Infections:* Trachoma, keratitis, uveitis*
  - *Trauma*:* Foreign body, sports injuries
  - *Tumors:* Retinoblastoma
  - *Degenerative:* ROP, R. pigmentosa, detachment
  - *Vascular:* Retinal vein occlusion*
- ***CNS disorders***
  - *Infections:* Encephalitis, meningitis
  - Head injuries*
  - *Vascular*:* Strokes, migraine, raised ICP
  - *Tumors:* Craniopharyngioma, optic glioma
  - *Degenerative:* Storage disorders, leukodystrophies
- ***Psychogenic**** (Hysteria/conversion reaction)

may lead to acute loss of vision.
ROP: Retinopathy of prematurity

Under the *Indian Disability Act 2016*, loss of vision is defined as:

Total Blindness with the inability to distinguish darkness from bright light in either eye, *or*

Low-vision with any of the following criteria:
- Visual acuity not exceeding 6/18 or less than 20/60 up to 3/60 or up to 10/200 (Snellen) in the better eye with best possible corrections.
- Limitation of the field of vision subtending an angle of less than 40 degree up to 10 degree.

26.3.2 AMBLYOPIA

Amblyopia denotes "*decreased visual acuity due to lack of a clear retinal image and cortical suppression of the defective image*, during developing phase of vision". It may be unilateral or bilateral. Important characteristics of amblyopia (d/d with amaurosis, i.e. blindness) are as follows:

Amblyopia occurs only in young *visually immature* children (<10 years), due to factors which prevent normal development of visual acuity, i.e. misaligned visual axis (*strabismic amblyopia*), high refractive errors (*ametropic amblyopia*), unequal refractive errors in two eyes (*anisometropic amblyopia*) and media opacities, e.g. cataract (*deprivational amblyopia*).

It is usually asymptomatic, not associated with sufficient organic abnormality to explain diminished visual acuity on ophthalmic examination.

It is rapidly reversible in young children if causative factor is eliminated, but becomes permanent in longstanding cases.

Other common visual image defects include:

Nyctalopia (Night-blindness) indicates defective function of the rods, seen in vitamin A deficiency, early retinal disorders, e.g. retinitis pigmentosa and as a hereditary condition.

Diplopia (Double-vision) indicates mal-alignment of visual axis, seen in strabismus, myasthenia gravis, orbital asymmetry, e.g. proptosis and raised ICP.

26.3.3 REFRACTIVE ERRORS

Normal eye is *Emmetropic*, i.e. parallel rays of light are adequately refracted by ocular media, i.e. lens to focus exactly on retina, without accommodation efforts.

Ametropia denotes altered location of image formation due to refractive errors and includes: (a) hypermetropia, (b) myopia, (c) astigmatism, and (d) anisometropia. Refractive errors may be tested in children—(a) *Objectively* by retinoscopy—focusing a beam of light on retina, through various lens powers in front of eye, and (b) *Subjectively* by asking an older child to read a *Snellen's chart*, first without lenses and than through various lens powers to identify the lens with clearest image.

Retinoscopy is essential in children <3 years and preferable in older children. Refractive errors in a suspected case should be tested both, before and after instillation of cycloplegic agents, to exclude the effect of accommodation.

Hypermetropia is optically characterized by image formation *behind the retina*, due to: (a) decreased orbital size, (b) inadequate corneal refraction, e.g. in flattened cornea, (c) inadequate lenticular refraction due to reduced refractive power or posterior dislocation of lens.

Children are physiologically hypermetropic till 5–6 years of age due to smaller orbit (~3 diopters at birth). Unlike hypermetropic adults, hypermetropic children have difficulty to see both distant as well as near objects and tend to use excessive accommodation to increase lens thickness and decrease its focal length to ensure image formation at retina.

Consequently, eyestrain, headache, squinting while reading and eye rubbing is common. Severe cases may develop *strabismus* due to excessive use of accommodation and *deprivation amblyopia* due to cortical suppression of image from the affected eye.

Management aims to bring forward the visual image on retina without accommodative efforts, using *convex lenses* of suitable strength. As hypermetropia tends to

improve with age due to increasing orbital size, lenses of lesser strength are required gradually and sometimes, it is even possible in eliminate the needs for glasses.

Myopia (Near-sightedness) is optically characterized by image formation *before the retina*, due to: (a) larger orbital size, e.g. in glaucoma, (b) increased corneal refraction, e.g. in keratoconus, and (c) increased lenticular refraction due to anterior dislocation of lens. It is uncommon in early childhood (except preterms) and with increasing incidence and severity in school age. High myopia is usually hereditary with strong family history.

Earliest indicator of myopia is tendency to read by keeping the books close to eyes, frowning and squinting. Amblyopia is uncommon due to later onset of error.

Management of myopia involves correction of refractive error by *concave lenses* of suitable strength. Severe myopia tends to increase with age, sometimes complicated by retinal detachment.

Astigmatism is optically characterized by *variable refractory powers in various meridians*, leading to distortion of images. Most cases are caused by irregular curvature of cornea *or* lens.

While mild astigmatism is common and often asymptomatic, more severe cases use excessive accommodation to create a pin-hole effect for better image, leading to eyestrain, headache, frowning or squinting.

Correction of astigmatism requires use of *cylindrical lenses*, as early as possible to prevent amblyopia.

Anisometropia denotes significant *differences in refractive states of two eyes*, leading to disuse of more affected side and consequent amblyopia.

26.3.4 STRABISMUS (SQUINT)

Strabismus, i.e. *misalignment of the gaze,* is one of the commonest ophthalmic problems, present in ~4–5% of under-5 children. Early detection and treatment of strabismus is essential to prevent secondary amblyopia and psychological stress.

Types: States of ocular balance may be divided in three types:

Orthophoria, i.e. ideal and exact ocular balance between two eyes with synchronized image formation in all directions and distances of gaze, which is seldom present in children.

Heterophoria (Latent squint), which manifests only in stress situations, e.g. fatigue, illnesses or after covering the normal eye. Some degree of heterophoria is common in normal children, though large heterophoria may lead to diplopia, headache and eye-strain.

*Heterotropia (*Manifest squint) is persistent misalignment of gaze, in one or more directions of gaze.

Heterophoria or heterotropia is further classified according of the direction of deviation in squinted eye as: (a) *esophoria/esotropia* or convergent squint (commonest type), (b) *exophoria/exotropia* or divergent squint, (c) *hyperphoria/hypertropia*, i.e. upward deviation, and (d) *hypophoria/hypotropia*, i.e. downward deviation.

Etiology of strabismus may be divided into:

Non-paralytic *(Concomitant) squint*, due to ocular or visual defects, e.g. refractive errors in involved eye, is more common in children.

Paralytic *(Non-concomitant) squint*, due to weakness of extraocular muscles is rare, caused by: (i) congenital neuromuscular abnormality, (ii) traumatic neuromuscular damage, e.g. in birth injury or basal skull fractures, (iii) CNS infections/tumors, (iv) toxic neuropathies, e.g. diphtheria, lead poisoning, etc.

Consequences: Primary optic consequence of strabismus is *diplopia* due to misalignment of two visual axis, i.e. formation of two separate images on retina. However, secondary optic response to diplopia varies according to the age of child.

A visually immature child (<5–6 years) tends to suppress one of the two diplopic images at cortical level *or* by maintaining abnormal head-position, leading to *amblyopia* in affected eye.

An older child is usually unable to achieve this *visual suppression* and remains diplopic, with consequent headache and eye-strain.

Diagnosis of squint may be made by:

Corneal reflex test (*Hirschberg's test*), particularly useful in uncooperative children or those with poor visual fixation. When a torchlight is projected on the cornea of both eyes simultaneously with child looking directly towards the source, light reflection on both the cornea should be symmetrical and centrally placed. In strabismus, reflection is asymmetrical and off-center in affected eye. In *Krimski method*, prisms are placed over one or both eyes to assess the amount of prism needed to align reflections, i.e. degree of squint.

Cover test is more useful to detect latent squint, though requires child's cooperation and reasonably good vision. In *Cover-uncover test*, child is asked to focus on an object with both eyes. Subsequently, when one eye is covered, movement of uncovered eye to readjust the image indicates latent squint in uncovered eye. Similar procedure is repeated with other eye. In another method, i.e. *Alternate-cover test*, examiner rapidly covers and uncovers each eye alternately like a windshield wipers. Rapid movement of eye, as it is uncovered, indicates ocular deviation. Cover tests should be performed for both distant and near vision fixation and in different gaze positions to detect latent squint or heterophoria.

Assessment of refractive errors and other ocular or neurological conditions is necessary to identify the cause of strabismus.

Management of strabismus aims to:

- Eliminate causative factors, e.g. refractive errors
- Encourage use of affected eye to prevent secondary amblyopia, by covering the normal eye for few weeks (occlusion therapy)
- Correct visual axis misalignment by orthoptic exercises and surgery in selected cases.

26.3.5 NYSTAGMUS

Nystagmus, i.e. *rhythmic oscillation of one or both eyes*, is physiological in newborns due to immature visual fixation *or* during certain stimuli, i.e. ear irrigation.

Etiology: Pathological nystagmus may be congenital or acquired, due to—(a) *defective visual perception* in ocular or visual pathway disorders, (b) *defective neurological control* of extraocular movements, e.g. cerebellar or brain-stem lesions, and (c) *defective reflex control* of extra-ocular movements, e.g. vestibular lesions. Common causes of nystagmus are given in **Table 26.16**.

Clinical evaluation of nystagmus requires recording the: (a) frequency, (b) amplitude, and (c) direction of oscillations as well as effect of gaze-direction on them.

Two most important types of pathological nystagmus are *pendular nystagmus*, i.e. equal velocity movements on both directions and *jerky nystagmus*, i.e. slow movement in one direction and rapid movement in other direction.

TABLE 26.16: Common causes of nystagmus

Physiological

- Newborns
- *Physiological stimuli:* Optokinetic, caloric test

Pathological

- Congenital nystagmus
- *Ocular (sensory):* Cataract, retinal disease
- *Vestibular:* Labrynthitis, drugs
- Neurological disease
  - *Cerebellar lesions:* Cerebellitis, tumors, drugs
  - *Brain-stem lesions:* Arnold-Chiari syndrome
  - Lesions of optic chiasma, e.g. tumors
  - *Others:* Spasmus nutans

Important diagnostic features of nystagmus are as follows:

- *Physiological nystagmus* is slow, low-amplitude with not more than 3–4 oscillations at a time.
- *Horizontal jerky nystagmus* is usually vestibular in origin, with quick component away from lesion and tends to disappear after gaze fixation.
- *Sensory or ocular nystagmus* is usually asymmetrical (mono-ocular) and latent, manifesting only when the better eye is covered.
- *See-saw nystagmus* (one eye rises and other falls) is usually seen in Lesions of optic chiasma.
- *Horizontal nystagmus in a particular gaze*-direction indicates vestibular or brain-stem lesion, while Horizontal nystagmus irrespective of gaze-direction (gaze-paretic) indicates cerebellar disease.
- *Vertical nystagmus* almost always indicates cerebellar or brain stem lesions.

A detailed ophthalmic and neurological evaluation is essential in all cases of pathological nystagmus, to exclude serious neuro-ocular disease.

Other important variants of oculomotor disorders include:

Opsoclonus, i.e. spontaneous, non-rhythmic, multi-directional, chaotic movements of eyes (*agitated eye*) may be seen in encephalitis and neuroblastoma.

Ocular dysmetria is akin to limb dysmetria, i.e. over-shooting or under-shooting of visual fixation on rapid gaze changes with corrective oscillations, seen in cerebellar disease.

Ocular bobbing, i.e. up and down jerky movements of eyes indicates pontine disease.

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CHAPTER

27

Critical Care

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27.1 CARDIOPULMONARY RESUSCITATION

Unlike adults, Cardiopulmonary arrest (CPA) in children is rarely a sudden event, often preceded by progressive deterioration of respiratory or cardiovascular functions. Prompt recognition and management of impending respiratory failure and shock may obviate the need of cardiopulmonary resuscitation (CPR) in most cases.

Depending on the emergency needs and availability of technical expertise/facilities, CPR may be broadly divided into two different protocols or processes:

a. **Basic life-support (BLS)** is a series of *sequential* measures in the emergency management of usually *sudden* CPA due to unforeseen causes, e.g. injuries and foreign bodies, with limited resources and technical knowledge, till advance life support (ALS) is possible. These situations usually arise outside the hospital setting and BLS may be administered even by a lay person.

b. **Pediatric advanced life-support (PALS)** usually takes place in health-care settings, when CPA is *usually gradual*, following a premorbid condition. Many trained rescuers are available and multiple resuscitative measures can be taken *simultaneously* and in parallel.

Following discussion includes revised protocol of standard pediatric life-support measures, recommended by American Heart Association in 2020 and accepted as the *standard of BLS and PALS* throughout the world.

27.1.1 PEDIATRIC BASIC LIFE SUPPORT

Primary aim of BLS is to restore and maintain vital functions till advanced life-support can be instituted, in order to preserve the organ viability and to help the *return of spontaneous circulation* (ROSC). Evaluation and interventions in BLS are performed simultaneously in the following sequence : (a) assessment , (b) circulation, (c) airway, and (d) breathing.

Conventionally, BLS was a sequential actions to restore airway, breathing and circulation in that order, often termed as *ABC* of resuscitation. However, studies have shown that effort to restore the circulation by chest compressions must precede breathing support for better survival and outcome.

Accordingly, the *approach has changed from ABC to CAB since 2015,* i.e. *circulation, airway and breathing, in that order*. However, this change should not be construed as lesser importance to breathing support, which should begin within 20 seconds of initiation of the chest compressions.

Important steps in BLS **(Fig. 27.1)** based on the current recommendations 2020, are as follows:

Step 1. Ensure safety of the patient and rescuer, as most of the emergency events requiring BLS happen out-of the hospital, e.g. on roads. Move the victim to a safer place if possible.

Step 2. Assess the response by gently tapping the child and asking a simple question, e.g. "Are you OK ?". If the child is responsive, check for external injuries and need for medical assistance. Call for the help and alert the emergency response system without leaving the victim for long time. Do not move the child, if a spinal injury is suspected. Children with respiratory distress often assume a position that maintains airway patency and optimizes ventilation. Allow these cases to remain in a position that is most comfortable.

Step 3. Assess the breathing by looking at the victim.

- If breathing is normal, no resuscitation is required except close supervision till the help arrives. Turn the child, if unconscious, in the recovery position **(Fig. 27.2)** to facilitate airway patency and decrease risk of aspiration. However, do not move the victims with suspected spinal injury.
- If the child is non-responsive or not breathing (or only gasping), it should be assumed that cardiac arrest is present and resuscitation is required.

Step 4. Assess the pulse by palpating a peripheral pulse (brachial in infants, femoral/carotid in older children) for 10 seconds.

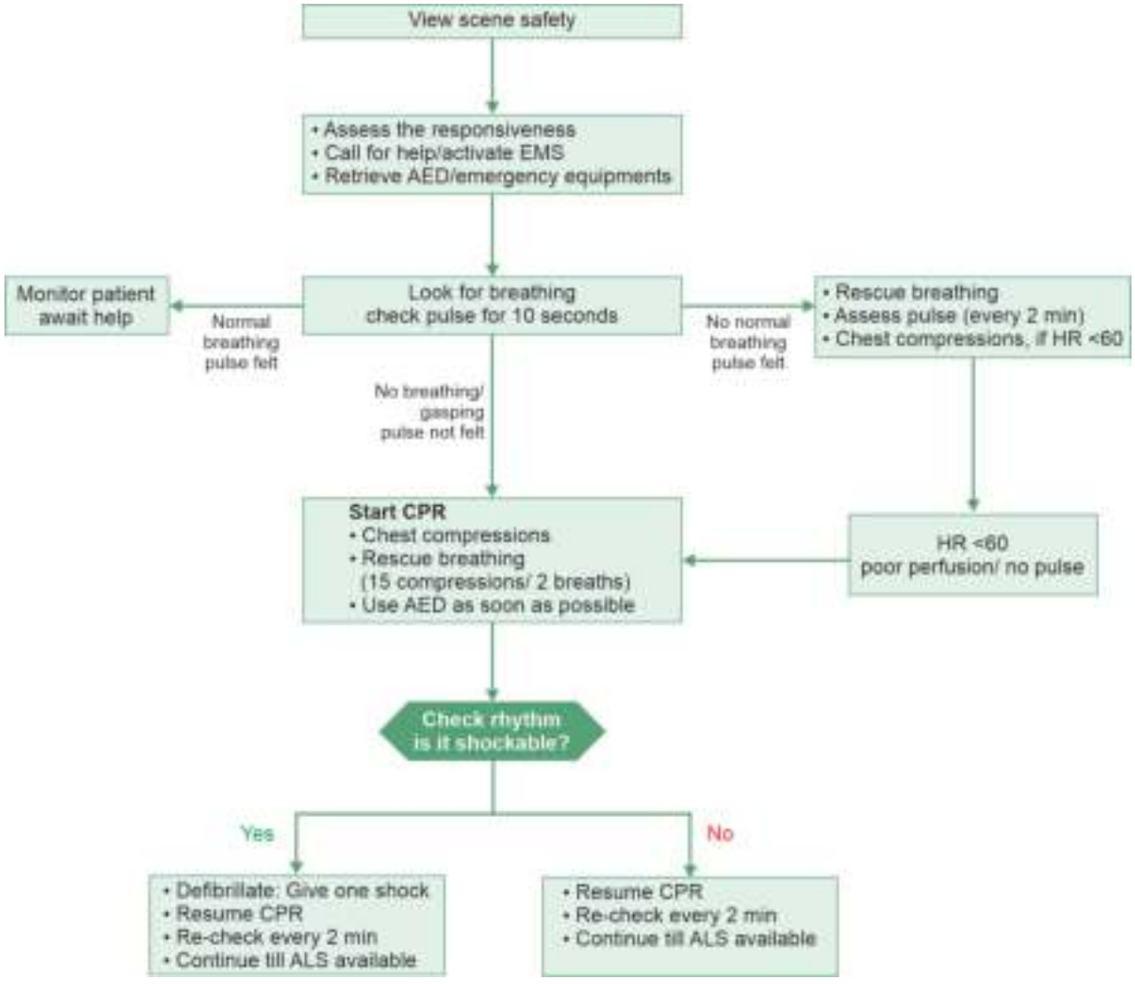


Fig. 27.1: **Basic life support algorithm.**

Based on AHA/AAP guidelines 2020.

Fig. 27.2: **Recovery position.**

- In absence of the pulse or pulse rate <60 minutes, begin chest compressions (Step 5), along with rescue breathing (step 6).
- In cases with pulse rate >60/min, begin rescue breathing @ 12–20/minutes (Step 6). However, if pulse rate drops <60/minutes with signs of poor perfusion, begin chest compressions (Step 5).

Step 5. Chest compressions. High-quality chest compressions generate blood flow to vital organs. Chest compressions are indicated if pulse is absent or pulse rate is <60/minutes. Some important considerations during chest compressions are as follows:

- Place the child on a firm surface in supine position.
- Use *Two-finger technique* in infants, unless a second rescuer is present when *Two-thumb chest encircling technique* is preferable **(Fig. 27.3)**.
- In older children, use the heel of one hand or two hands **(Fig. 27.4)** with two-hand technique being preferable due to less rescue fatigue.
- Compress the sternum ~2 fingers below the intermammary line in infants and over lower half of the sternum in older child. Xiphoid cartilage or ribs should never be compressed to avoid internal injury.
- Depth of compression is a major determinant of the efficacy of chest compressions and should be at least one-third of the anterior–posterior diameter of the chest, i.e. ~4 cm in infants and 5 cm in children.
- Rate of the chest compression should be ~100–120/minutes.

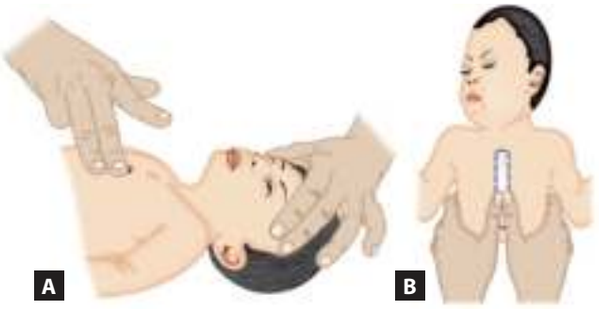


Fig. 27.3A and B: **Chest compressions in infant: (A) Two-finger technique; (B) Two-thumb technique.**

Fig. 27.5: **Head tilt-Chin lift maneuver.**

Fig. 27.4: **Chest compressions in older child.**

Fig. 27.6: **Jaw-thrust maneuver.**

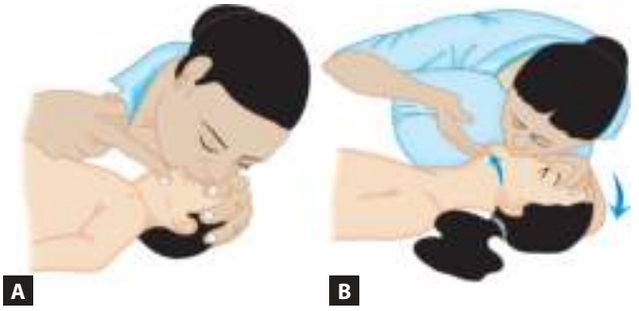
- After each compression, chest should be allowed to recoil back to normal to allow adequate venous return, before next compression.

Step 6. Open the airway and ventilate. After 15 compressions, give two rescue breaths, after opening the airways.

Airway obstruction may be due to posterior displacement of tongue, mucus plug/ foreign body in airways or abnormal neck position. *Head-tilt-Chin-lift maneuver* **(Fig. 27.5)** is recommended or opening of the airways in both injured and uninjured victims. Use *Jaw-thrust maneuver* **(Fig. 27.6)** without head-tilt, if spinal cord injury is suspected. Gentle exploration of oral cavity to remove mucus plug or foreign body may be useful.

Rescue breathing aims to support ventilation, till mechanical help arrives. Some important considerations during *rescue breathing* are as follows:

- Use mouth-to-mouth and nose technique in infants and mouth-to-mouth technique in older children **(Fig. 27.7)**.
- Ensure proper air-seal between rescuer's mouth and victim's mouth. Pinch the nose, if it could not be covered by rescuer's mouth.



Figs. 27.7A and B: **Rescue breathing in: (A) Infant; (B) Child.**

- Each rescue-breath must last ~1 seconds. Slow delivery of rescue breath is important to prevent barotrauma and gastric distension.
- Pause after each breath and inhale deeply (rescuer), to maximize Oxygen concentration.
- Observe movement of the chest wall, during each rescue breath. Reposition the head, make a better seal, and try again, if chest does not rise adequately during rescue breath. Consider the possibility of foreign body if chest expansion is poor despite proper technique and repositioning.

Barrier devices to decrease the risk of infection during mouth-to-mouth breathing have not been found useful for this purpose and may increase the resistance to airflow.

Bag and mask ventilation is preferred over mouth-to mouth rescue breathing, if available, discussed in PALS section.

Step 7. Coordinate chest compressions and ventilations at the ratio of 15:2. However, such coordination is not necessary if an advanced airway is in place. In such cases, one rescuer continues to deliver at least 100 compressions/minute without pauses for ventilation, while another one delivers rescue breaths @ 8–10 breaths/min. Re-evaluate after every 2 minutes to decide about the need for further continuation.

Step 8. Defibrillation. Ventricular fibrillation can be the cause of sudden collapse, e.g. during sport events, or may develop during resuscitation attempts, presenting with pulse-less arrest. These cases need immediate defibrillation. If possible, all cases who do not respond to compression-ventilation cycles for 2 minutes must be assessed for need of Automated External Defibrillators (AED).

In cases with shockable rhythm, deliver a defibrillation dose of 2 J/kg, to be repeated as 4 J/kg if required. Coordinate chest compressions and shock delivery to minimize time-gap between compressions and shock and resume resuscitation, beginning with compressions, immediately after shock delivery.

In cases with non-shockable rhythm, continue compression-ventilation till help arrives.

Step 9. Activation of nearest emergency medical system. Nearby center, equipped with advanced life support facilities, should be alerted as soon as possible with complete details of—(a) location of emergency with contact telephone number, (b) actual event with expected number of casualties, (c) general condition of victim/s, to requisition help for BLS and transport, as well as to prepare them for emergency arrival.

CPR IN SPECIFIC SITUATIONS

Although abovementioned principles of CPR are applicable in most cases, following clinical situations warrant specific precautions, as follows:

Foreign body airway obstruction (FBAO) is a common emergency in pre-school children, to be suspected in any child with sudden respiratory distress, coughing, gagging, stridor or wheezing. Although removal of the foreign body may be life-saving in these cases, attempts should be made only if foreign body was witnessed or strongly suspected. For the purpose of resuscitation, FBAO is classified as *mild*, if victim can make a sound; or *severe*, if she/he cannot.

- In case, the foreign body is visible, remove it. However, *Blind finger sweeps should not be performed*, as foreign body may be pushed back further into airway.
- In cases of mild FBAO, do not interfere and encourage spontaneous cough to clear the airway.
- In cases with severe FBAO, use *Back-blows and chest-thrust maneuver* in infants and *Heimlich maneuver* in older children, discussed as below. Heimlich maneuver with abdominal thrusts is not recommended for infants, due to risk of abdominal injury.

Back-blows and chest-thrust maneuver is used in *infants* to expel unseen foreign body. Back blows are delivered by resting the child over rescuer's arm in prone, head-low position and giving five forceful blows between shoulder blades with heel of the hand. After careful turning-over the baby, Subsequent chest thrusts are delivered by placing him on rescuer's thighs in supine, head-low position and giving five quick downward thrusts by two fingers over lower half of sternum. These steps are repeated until foreign body is expelled *or* it becomes visible and can be removed by tongue-jaw lift maneuver. Else, rescue breathing should be given, before another attempt **(Fig. 27.8)**.

Heimlich maneuver is used in *older children* to expel unseen FB, by giving abdominal thrusts. *In a conscious child*, these thrusts are delivered in standing position, by encircling the child from behind placing thumb-side of one fist between navel and xiphoid process > grasping the fist with other hand to deliver a series of quick upward thrusts till foreign body is expelled becomes visible and may be removed by tongue-jaw lift maneuver. **(Fig. 27.9)**. Else, rescue breathing should be given before another attempt *In unconscious child*, abdominal thrusts are delivered in supine position at the same site **(Fig. 27.10)**.

Trauma: Important additional considerations during resuscitation of a trauma victim are as follows:

- Anticipate airway obstruction by dental fragments, debris, etc.
- Stop external bleeding with direct pressure.
- Minimize body movements in cases with suspected spinal injury and immobilize at least the torso on immobilization board, if possible.

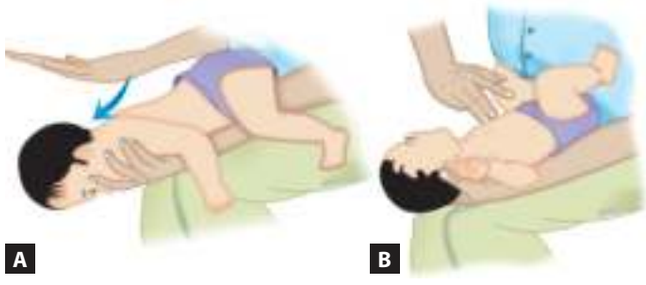


Fig. 27.8A and B: Back blow (A) and chest thrust (B) maneuver to relieve airway foreign body obstruction in infants.

Fig. 27.9: **Heimlich's maneuver.**

Fig. 27.10: **Abdominal thursts for foreign body removal in lying down position in unconscious child.**

- Don't use *Head-lift-chin-tilt procedure* in suspected cranio-cervical injury. Instead, Jaw-thrust maneuver may be used to open airways in these cases.

27.1.2 TRANSPORT OF SICK CHILD

Although developed countries have separate critical-care teams for transport of sick children from the site of emergency or primary care to nearest pediatric intensive care units (PICUs) or tertiary trauma centers, such facilities are almost non-existent in India. However, following steps should be followed scrupulously during transport of these cases:

a. **Advance notification** to the nearest PICU or trauma center on phone, with complete information regarding patient's cardiopulmonary status, suspected cause of injury/indication for transfer and the expected time of arrival at receiving unit. Consent of the receiving unit, along with the name of contact person should also be obtained prior to transfer. Copy of all patient records, including laboratory reports should accompany the patient for review by receiving unit.

b. **Pre-transport stabilization** with BLS measures as discussed earlier. As far as possible, the patient should be transported with a secure venous access for fluids/drugs administration during transport. It is also necessary to ensure an adequate and patent airway, along with best possible ventilatory support, e.g. oxygen or bag/mask ventilation, before transport.

Children with suspected spinal injuries need adequate splint immobilization to avoid aggravation of injury.

c. **Mode of transport:** Choice for the mode of transport depends on urgency, patient's status, travel-distance and feasibility. Unlike developed countries, where air transport of sick cases is frequently available, road transport is the norm in India, using hospital ambulances. All tertiary care centers are expected to have a well-equipped ambulance for pickup and transfer of critically sick children. Some non-governmental organizations also provide such facilities on humanitarian or payment basis.

As most of these vehicles are usually designed and equipped for adult transport, it is important to ensure adequate supply of essential drugs and equipment, e.g. endotracheal tubes, etc. for pediatric patients, before transport.

d. **Experienced transport team:** Unlike specially trained transport teams in developed countries, critically sick children in India are usually accompanied by paramedical personals with a little experience in pediatric resuscitation. Hence, It is desirable that a trained pediatric staff accompanies the patient during transfer, well-experienced in at least BLS measures.

e. **Actual transport:** A baby should be constantly monitored during transport for vital signs and need for resuscitative procedures, by accompanying medical/paramedical person. However, as actual resuscitation is often difficult in a moving transport vehicle, the aim should be to use shortest and fastest route to minimize patient's distress and need for resuscitative procedures.

f. **Acceptance of transfer:** Receiving unit, pre-informed by referring unit, must be well-prepared to accept the case on arrival with appropriate administrative formalities, suitable intra-hospital transport, e.g. stretchers and resuscitative equipments. Accompanying person should supply details of patient's status during transport as well as medical records from referring unit.

g. **Post-transport follow-up:** The referring unit should be contacted by receiving unit to inform status of the patient *on arrival* and enquire about further medical details. The receiving unit is also responsible to provide subsequent follow-up about the case, including ultimate outcome, to the referring unit.

27.1.3 PEDIATRIC ADVANCED LIFE SUPPORT (PALS)

Pediatric advanced life support (PALS) is a more organized approach than BLS towards the evaluation and management of CPA, before, during and after the arrest. Unlike *sequential* actions in BLS, resuscitative measures in PALS are applied *simultaneously and concurrently*, as it usually takes place in hospital environment with many rescuers and technological support.

Pediatric chain of survival includes 6 components—(1) early recognition and prevention of cardiac arrest, (2) activation of emergency response, (3) high quality cardiopulmonary resuscitation, (4) advanced resuscitation, (5) post-arrest care, and (6) recovery.

Important ***components* of PALS** include—(1) basic life support, (2) use of equipments and techniques to establish and maintain oxygenation, ventilation and perfusion, (3) clinical and ECG monitoring for arrhythmia and management, (4) establish and maintain vascular access, (5) identify and treat reversible causes of cardiopulmonary arrest, (6) emergency treatment of cardiac and respiratory arrest, and (7) treating patients with trauma, shock, respiratory failure and other pre-arrest conditions.

While important aspects of these components have been discussed here sequentially, PALS involves concurrent efforts on all fronts, as follows:

A. Initial assessment: Most cases requiring PALS are already in hospital, under constant monitoring and usually deteriorate gradually. Cases with acute CPA are usually managed by BLS, discussed earlier, before transfer to the hospital. Hence, it is often possible to anticipate the need for resuscitation in these cases, based on clinical and laboratory assessment.

Initial assessment about the need and strategy of the resuscitation largely depends on five vital parameters, often termed as **ABCDE**, i.e. ***A***irway, ***B***reathing, ***C***irculation, ***D***isability in terms of neurological functions and ***E***xposure or visual search for bodily injuries. A quick history at this stage also helps to look for special danger signs and decide course of resuscitation. Important pointers towards the need of PALS usually relate to signs of:

- Airway obstruction, e.g. stridor, poor chest expansion or breath sounds, etc.
- Respiratory failure, e.g. tachypnea, dyspnea, grunt, cyanosis, apnea/gasp, etc.

TABLE 27.1: Normal range of vital signs in children

Age	*HR (min)*	*RR (min)*	*BP* (mm Hg)*
0–3 mo	100–150	35–55	65/45
3–6 mo	90–120	30–45	70/50
6–12 mo	80–120	25–40	80/55
1–3 year	70–110	20–30	90-55
3–6 year	65–110	20–25	95/60
6–12 year	60–95	14–22	110/60
> 12 year	55–85	12–18	110/65

*Lowest of the range for systolic/diastolic BP.

- Circulatory failure, e.g. tachycardia, cold extremities prolonged capillary refill time, weak pulse, hypotension, etc.
- Neurological dysfunction, e.g. altered sensorium, dilated and slow-reacting pupils, flaccid tone, decerebrate/decorticate posture, etc.

Table 27.1 provides acceptable ranges for normal vital signs, i.e. heart rate (HR), respiratory rate (RR) and blood pressure (BP), at various ages, to identify the need for intervention. However, three simple rules are:

- RR should never by >60/minutes for sustained period.
- HR should never be > 3 times of RR.
- BP should never be <60 mm Hg in newborns, <70 mm Hg in infants, < 70 + (2 x Age) in 1–10 years age or <90 mm Hg in older children.

B. Effective airway maintenance, may require—(a) correct positioning, as discussed previously under BLS, (b) airway suction, (c) Oro-/naso-pharyngeal airways, *or* (d) endotracheal intubation/Tracheostomy. The fact that pediatric airways differ from adult airways on several aspects **(Table 27.2)** has led to evolvement of specific PALS guidelines, which should be followed meticulously during respiratory resuscitation. Some important considerations in airway maintenance are as follows, while procedural/instrumental details are discussed in Ch 32.4.

Airway suction in older children requires use of a portable foot-operated/electric suction machine *or* central suction system. Oral mucus extractors are not much effective beyond the neonatal period. A sterile/

TABLE 27.2: Anatomical peculiarities of pediatric airway

- Smaller airway diameter, easily blocked by edema/mucus
- Large tongue with risk of posterior displacement and airway block
- Relatively cephalad larynx with acute angle between tongue base and glottic opening*
- Short-narrow epiglottis at sharper angle with trachea*
- Lower anterior attachment of vocal cords*
- Funnel-shaped larynx, narrowest below the vocal cord at the level of non-distensible cricoid cartilage*

*Leading to intubation difficulties

disposable flexible suction catheter of *Fr 8* (Fr 5 or 6 in newborns < 3 kg) is preferable and less traumatic, except to remove thick secretions or particulate matter by rigid catheter. Important consideration during suction are:

- Optimum suction force should be ~80–120 mm Hg (vs ~30 mm in newborns),
- Suction time should not exceed >5 seconds at one attempt. Intermittent O_2 supplements are necessary between multiple attempts to prevent hypoxia.
- Heart rate should be monitored to detect significant bradycardia, due to vagal stimulation.

Important complications of suction are—(a) oral mucosal trauma, (b) nosocomial infection and rarely, (c) sudden CPA due to vagal stimulation.

Airways: Different devices used to maintain patency of airways include:

Oropharyngeal airway is a curved rubber device to prevent glossoptosis and ensure clear airway/suction channel **(Fig. 32.10)**. Proper size may be estimated by placing its flange at the corner of mouth, when tip should reach the angle of mandible. *It should not be used in a conscious child.*

Nasopharyngeal airway is a short disposable rubber/plastic tube, better tolerated in *conscious* patients, though not used frequently. It is inserted via nostrils with proper length being the distance between tip of the nose and tragus. Use of fabricated nasal airways by cutting an endotracheal tube, should be avoided due to risk of accidental slippage beyond nares, unless an adapter is used.

Laryngeal mask airway (LMA) may be used to ensure patent airway and support ventilation, only if Bag and Mask Ventilation is unsuccessful and Endotracheal intubation is not possible. However, difficulty in its placement and higher incidence of complications precludes use of LMA in young children.

Endotracheal intubation is indicated in presence of—(a) airway obstruction, (b) poor response to bag-mask ventilation, (c) need for mechanical ventilation. Important considerations in endotracheal intubation are:

- A sterile endotracheal tube of proper size (uncuffed tubes of 2.5-3 in preterms, 3-3.5 in term newborns, 3.5-4 mm in infants and 4+(age/4) in older children) should be inserted under laryngoscopic visualization to the desired depth from alveolar margins *(Age/2+12; in cm)* up to mid-trachea.
- Despite the lower risk of aspiration, cuffed endotracheal tubes are rarely used in children as normal anatomically-narrow cricoid cartilage itself provides a functional cuff. If used, size should be 0.5 mm less than uncuffed tubes.
- A straight laryngoscopic blade *(Miller type)* is preferred in infants/young children, while curved blade *(MacIntosh type)* is preferable > 8–10 years.
- IPPV with 100% oxygen via bag/mask should be given before and between intubation attempts, to prevent prolonged hypoxia. Each intubation attempt should not last for >30 second. Baby should be constantly monitored for bradycardia and cyanosis/pallor to prevent severe hypoxia.
- *Post-intubation*, the tube should be secured and its position and patency should be checked frequently to ensure adequate bilateral air-entry in lungs by auscultation. Position of the tube may also be checked by chest skiagram and $ETCO_2$ monitoring. Pulse oximetry is unreliable as SaO_2 may not decline for over 3 minutes, even without effective ventilation. Repeated suction are required to maintain tubal patency.
- If an intubated patient's condition deteriorates consider ***D**isplacement of the tube, **O**bstruction of the tube, **P**neumothorax or **E**quipment failure* (DOPE).
- For Endotracheal suction, catheter should not be inserted beyond the tip of endotracheal tube.

Tracheostomy is indicated in children with airway obstruction or difficult intubations, using a disposable tracheostomy tube. It serves the same purpose as intubation, with an added advantage of reducing dead space. However, disadvantages, e.g. infection, tracheal injury and subglottic stenosis, should be considered before tracheostomy decision.

C. Effective ventilatory support depends on the status of spontaneous breathing efforts and include: (a) oxygen supplementation in children with adequate spontaneous breathing, and (b) manual (Bag and mask) or mechanical ventilatory assistance in cases with absent/feeble breathing efforts.

Some important considerations in ventilatory support are as follows, while procedural and equipmental details are given in Ch 31.4 and 27.2.

Oxygen therapy aims to deliver 100% oxygen during the resuscitation till circulation is established, and then to raise O_2 content in inspired air (FiO_2) to maintain PaO_2 >60–70 mm Hg or SaO_2 > 94%, via: (a) *low-flow devices*, e.g. nasal catheters, prongs or face-masks, (b) *high-flow devices*, e.g. face-tents or oxygen-hoods, and (c) *bag/mask ventilation*.(Ch 32.4)

Efficacy of these devices varies according to the oxygen flow rate and amount of mixing with expired/environmental air **(Table 27.3)**.

Direct nasal devices are simple but least effective, potentially traumatic and cannot be used to deliver a flow rate of >2–4 L/minute due to nasal irritation. 100% oxygen can be truly delivered only by mechanical ventilation *via* endotracheal tube, though fairly high FiO_2 (>60–80%) may be achieved in spontaneously breathing child, by high-flow delivery (>10 L/minute) via face masks with reservoir/re-breathing bag.

TABLE 27.3: Common oxygen delivery devices

Device	*Flow (L/min)*	*FiO_2*
Nasal cannula	2–4	20–40%
Simple mask	4–6	30–40%*
Venturi mask	6–10	40–60%
Face tent	10–12	~40%
O_2 hood/tent	10–12	~80%
Bag-mask	Adjustable	100%

*up to 60–70%, if tight-mask and reservoir is used

Reservoir is a bag attached to the face-mask, which collects initial O_2-rich portion of exhaled air that remains in upper airways. During next breath, it is mixed with fresh oxygen, to enrich inspired air. Continuous pulse oximetry to monitor SaO_2 is advisable during CPR (Ch 27.4.4), in all cases.

Bag and mask ventilation (Manual resuscitator) is a simple method to deliver high-oxygen concentration, specially in children with inadequate breathing efforts till mechanical ventilation is arranged or during transport.

Common AMBU bag (*A*mbulatory *m*anual *b*reathing *u*nit) may be used to deliver—(a) *continuous positive airway pressure* (CPAP) ventilation by maintaining a constant pressure of ~5–10 cm H_2O over bag, or (b) *intermittent positive pressure ventilation* (IPPV) by active deflation, followed by self-inflation. Important considerations in bag-mask ventilation are as follows, while procedural/equipmental details are given in Ch 32.4.

- Proper supine position with slightly hyperextended neck (head-tilt, chin-lift) to keep the airway open.
- Proper-size, Snuggly-fitted face-mask, to minimize dead space and rebreathing of exhaled air.
- Proper-size resuscitation bag (450–1000 ml), to deliver a tidal volume of ~10-15 ml/kg.
- Proper pressure on the resuscitation-bag, just to raise the chest visibly but never to exceed 35–45 cm H_2O, except during initial resuscitation. Excessive pressure not only risks barotrauma but also impedes systemic venous return due to high intrathoracic pressure, thus reducing cardiac output and cerebral and coronary blood flow.
- Proper rate of 2 breaths/15 chest compressions during CPR and ~12–20 breaths/minutes post-CPR, with an inspiratory time of ~1 second/breath.
- Frequent check on air-entry into lungs and clinical signs to ensure adequate ventilation.

A self-inflating resuscitation bag (without oxygen source) delivers ~20% of FiO_2, which may be increased to ~30% if an oxygen source with a flow rate of ~10–12 L/min is connected; and ~60–80% if oxygen source as well as oxygen reservoir is connected. 100% oxygen can be delivered only if resuscitation bag is connected to endotracheal tube, instead of face mask.

Two-person bag and mask ventilation, with one rescuer maintaining the open airway with a jaw-thrust and tight mask-to-face seal and the other compressing the ventilation bag, is more effective than single-person method.

Main complication of bag and mask ventilation without endotracheal tube is gastric distension > regurgitation > aspiration, which can be minimized by inserting a nasogastric tube or ***Sellick maneuver*** (pressure on cricoid cartilage to occlude proximal esophagus).

Bag and mask ventilation is *contraindicated* in—(a) diaphragmatic hernia, or (b) suspected kerosene poisoning, where endotracheal intubation is mandatory, which may be attached to resuscitation bag.

Mechanical ventilation is indicated in children with established respiratory failure with specific indications, discussed in Ch 27.2.

D. Adequate vascular access: A reliable venous access is the crucial step in PALS, though temporary *intraosseous route* may be used for emergency fluid and drug administration, if venous access is not achieved in three attempts *or* 90 seconds (*see* Ch 32.3).

While central venous access is more secure for long-term use and to deliver irritant medicines, e.g. calcium, placement of central venous catheter is time consuming and needs experience, hence, not recommended as the initial route of vascular access in an emergency (also see Ch 27.4.3).

Some lipid-soluble drugs, e.g. adrenaline, atropine, naloxone, lidocaine, etc. may also be given intratracheally before IV access is obtained, in doses 10 times (for adrenaline, for others 2–3 times) of IV dose, diluted up to 5 ml of normal saline. Each intrathecal administration should be followed by 5 manual ventilations to ensure adequate absorption.

Lipid-insoluble drugs, e.g. sodium bicarbonate and calcium may injure the airway and should not be administered via endotracheal route.

E. Effective circulatory support: Circulatory insufficiency is an integral component of CPA and all children after initial ventilatory resuscitation should receive 20 ml/kg of IV ringer lactate or normal saline, before definitive assessment and treatment of shock (Ch 27.3). Dextrose-solutions should not be used for initial resuscitation, except in suspected/documented hypoglycemia, as they are poor volume expanders and may cause hyperglycemia and consequently, diuresis.

F. Monitoring: Constant monitoring is essential component of PALS for timely therapeutic decisions and includes: (a) clinical assessment of biophysical parameters, e.g. HR, RR and efforts, BP, and (b) relevant laboratory investigations, e.g. Blood sugar, ABG and electrolytes. Real-time non-invasive monitors, e.g. pulse-oximeter, have revolutionalized constant monitoring during PALS (Ch 27.4.4).

G. Treatment of complications: Three important and potentially fatal immediate consequences of CPA are: *Respiratory failure, Shock and arrhythmia*, of which first two are discussed in later chapters. Common medications used to manage these complications have been listed in **Table 27.4**.

Arrhythmias may develop during or immediately after CPR, usually due to **6Hs** (**H**ypoxia, **H**ypovolemia, **H**ypokalemia, **H**yperkalemia, **H**ypoglycemia and **H**ydrogen ions, i.e. acidosis) or **5Ts** (**T**rauma, **T**oxins, **T**emponade, **T**hrombosis and **T**ension pneumothorax), apart from drugs used in resuscitation. Although discussed in detail elsewhere (Ch 17.10), some important aspects of the management for common arrhythmias are as follows:

- **Bradycardia or bradyarrhythmias** are common rhythm abnormalities just before the arrest, which may prevent adequate circulatory resuscitation. Specific management involves chest compressions once the HR drops < 60/min with poor perfusion, followed by Adrenaline in non-responders (IV

TABLE 27.4: Common medications used in PALS

Adrenaline	IV 0.1 ml/kg (1:10000)
	ET 0.1 ml/kg (1:1000)
Adenosine*	0.1 mg/kg repeat 0.2 mg/kg
Atropine	IV 0.02 mg/kg
	ET 0.03 mg/kg (Min 0.1 mg)
Calcium gluconate 10%*	IV 1 ml/kg IV
Sodium bicarbonate	IV 1 mEq/kg
Amiodarone*	5 mg/kg (max 15 mg/kg)
Lidocaine*	IV 1 mg/kg
	>20–50 µg/kg/min
Naloxone	IV/ET 0.1 mg/kg
Magnesium sulphate	IV 25–50 mg/kg push
	(slow infusion in asthma)
Dextrose (10% or 25%)	0.5–1.0 gm/kg (5–10 ml/2–4 ml/kg)

*With cardiac/ECG monitoring

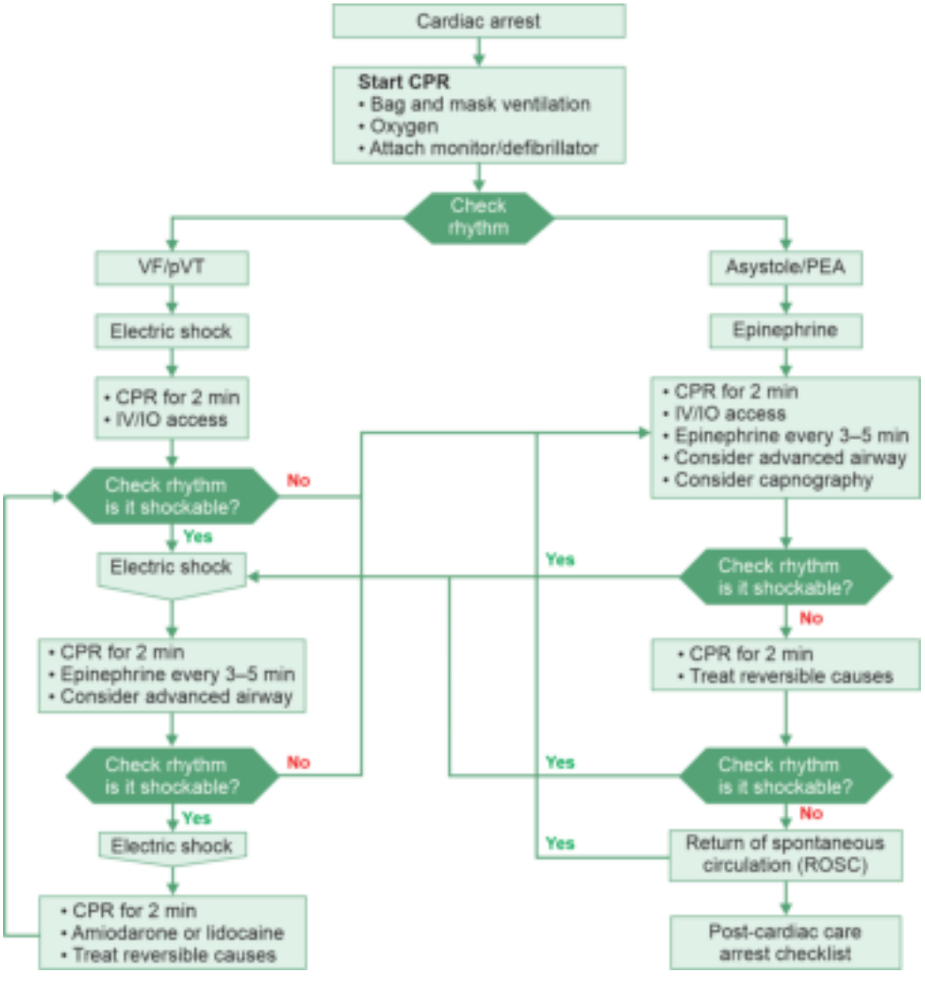


Fig. 27.11: Management algorithm: Cardiac arrest in children.

Based on AHA/AAP guidelines 2020.

0.1 ml/kg of 1:10,000 solution *or* IT 0.1 ml/kg of 1:1000 solution, repeated every 3–5 min) except in heart block or excessive vagal tone. Bradycardia due to vagal overtone is best treated with atropine (IV 0.02 mg/kg). Correction of causative factors is equally important.

- **Tachyarrhythmia** may originate in sinus node, atria (narrow-complex) or ventricles (wide-complex) and differentiation is important for management decisions. No specific treatment is required for sinus tachycardia except close monitoring. Supraventricular tachycardia needs immediate vagal maneuvers, followed by rapid 'push' adenosine infusion. Ventricular fibrillation or pulseless ventricular tachycardia develops in ~10% cases of pediatric CPA, which needs immediate defibrillation, along with simultaneous correction of causative factors.
- **Pulseless electric activity (PEA)** is a precursor of asystole, characterised by positive ECG activity without pulse or audible heart beat, also termed electro-mechanical dissociation. Treatment of PEA is same as that for asystole.

Recognition and Treatment of Cardiac Arrest

Unlike adults, cardiac arrest in children is usually due to non-cardiac causes, e.g. asphyxia, though some cases may develop acute CPA due to arrhythmias specially ventricular fibrillation.

High-quality CPR with effective chest compressions and breathing support, as discussed under BLS, is the key of management in these cases, along with emergency defibrillation in cases with shockable rhythm, i.e. ventricular fibrillation on ECG or cardiac monitoring.

Defibrillation in children requires two appropriate size paddles (8–10 cm, above 10 kg weight), one over the right upper chest and another over apex of the heart. Initial dose in children is 2 J/kg, which may be doubled in unsuccessful cases (Max 10 J/kg). After three failed attempts, child should receive epinephrine and CPR for 30–60 seconds before next effort, while amiodarone (IV 5 mg/kg bolus) or lidocaine (IV 1 mg/kg bolus) may be used after subsequent attempts.

Figure 27.11 provides an algorithm for resuscitation of a child in cardiac arrest, as per American Heart Association guidelines.

27.2 ACUTE RESPIRATORY FAILURE

Acute respiratory failure (ARpF) may be defined as - "a state of inadequate pulmonary functions to maintain adequate O_2 supply and CO_2 elimination' usually denoted by *PaO_2 < 60 mm Hg* on room air and/or *$PaCO_2$ >50 mm Hg*." Depending on the course, ARpF may be sudden or superimposed on chronic respiratory insufficiency.

Pathophysiology: Gaseous exchange in the lungs depends on three major functions—*ventilation*, *perfusion* and *diffusion* of gases. ARpF may develop due to abnormalities of any one *or* more of these functions, unless compensated by other components.

In children, capacity for this compensation is limited due to various developmental handicaps, e.g. (a) higher airway resistance, (b) poor chest wall compliance, (c) lesser lung volume, and (d) higher oxygen requirements (6–8 ml/kg *vs.* 3–4 ml/kg in adults).

Depending on the primary pathology, ARpF may be classified as:

a. ***Type I failure*** *(hypoxemic)*, due to impaired diffusion/perfusion, predominantly characterized by hypoxia (PaO_2 < 50 *mm Hg*), with/out hypercarbia,
b. ***Type II failure*** *(hypoxemic-hypercarbic)* due to impaired ventilation, predominantly characterized by hypercarbia ($PaCO_2$ >50 *mm Hg*), though hypoxemia is almost also present.

Note that the tissue hypoxia may also develop despite adequate pulmonary functions due to circulatory insufficiency (CCF, shock) *or* poor oxygen carrying capacity of blood (anemia). Hence, *a normal PaO_2 does not guarantee adequate tissue oxygenation*.

Etiology: Ventilatory insufficiency due to airway obstruction is the predominant cause of ARpF (Type II) in children, followed by intrinsic lung diseases (type I). Common causes of respiratory insufficiency and failure are listed in **Table 27.5**.

Clinically, important indicators of ARpF are:

a. *Signs of respiratory distress*, e.g. tachypnoea, dyspnoea, grunt, cyanosis or apnea.
b. *Signs of cerebral hypoxia*, e.g. restless/drowsiness, headache, convulsions, coma.
c. *Signs of circulatory compensation/failure*, e.g. tachy-/bradycardia, hypo-/hypertension, diaphoresis and terminal cardiac arrest.
d. *Signs of primary disease*, e.g. stridor, wheeze, lung signs, signs of bulbar palsy, etc.

Diagnostic evaluation: Confirmation and monitoring of ARpF revolves around the *arterial blood gas (ABG) analysis*

TABLE 27.5: Causes of acute respiratory failure

Primary ventilatory failure (Type II ARpF)
- Upper airway obstruction
  - *Intrinsic:* Malformations, croup, foreign body
  - *Extrinsic:* RPA, vascular rings, mediastinal mass
- *Pleural:* Empyema, pneumothorax, effusion
- *Restrictive lung:* Diaphragmatic hernia, scoliosis
- *Neurological disorders*
  - *Central:* CNS infections, head injury
  - Neuromuscular*, GBS, poliomyelitis

Primary gaseous exchange failure (Type I ARpF)
- *Lower airway obstruction:* Asthma, bronchiolitis
- *Intrinsic lung disease:* Pneumonia, atelectesis,
- *Impaired perfusion:* Pulmonary edema, shock-lung

GBS: Guillain-Barré syndrome; **RPA:** Retropharyngeal abscess
*due to diaphragmatic or bulbar palsy

TABLE 27.6: ABG analysis in acute respiratory failure

Parameter	*Normal*	*Type I*	*Type II*
PaO_2 (mm Hg)	90–100	<50	↓
$PaCO_2$ (mm Hg)	35–45	N/↓*	>50
SpO_2 (%)	>95%	↓↓	↓↓
pH	7.35–7.45	<7.35	<7.35
HCO_3 (mEq/L)	21–28	N/↓	N/↑

* due to hyperventilation

that provides valuable information regarding not only the blood-gas status but also of acid–base balance **(Table 27.6)**. Noninvasive monitoring techniques for ventilatory status, e.g. pulse oximetry (SaO_2) and end tidal CO_2 ($EtCO_2$) have revolutionized management of ARpF.

Other investigations in ARpF are necessary to assess the: (a) etiology, e.g. chest X-rays, (b) oxygen carrying capacity of blood, e.g. hemoglobin levels, and (c) extent of hypoxic damage, e.g. serum electrolytes, renal/liver function tests and coagulation profile (DIC is common).

Management of ARpF aims to ensure adequate air entry, alveolar ventilation, gaseous diffusion and oxygen carrying capacity of blood to deliver adequate O_2 at tissue levels and eliminate excess CO_2. It requires highly-skilled intensive care and includes:

- *Initial clinical evaluation* for
  - Spontaneous breathing efforts
  - Air entry into chest
- *Ensuring airway patency* by.
  - Positioning
  - Oro-/naso-pharyngeal airways
  - Airway suction
  - Endotracheal intubation/tracheostomy
- Oxygen delivery via.
  - Direct nasal cannula/catheter
  - Via face mask *or* oxygen tents
- Ventilatory assistance by.
  - Mouth-to-mouth (rescue) breathing
  - Bag and mask ventilation
  - Mechanical ventilation
- Continuous clinical and blood gas monitoring
- Treatment of primary cause
- Management of hypoxic tissue damage

A schematic approach towards management of established *or* impending ARpF is given in **Fig. 27.12**. While emergency measures, e.g. airway maintenance, oxygen supplementation and manual ventilator assistance are discussed in previous chapter, most cases ultimately require mechanical ventilation.

Mechanical Ventilation

While detailed description of modalities for mechanical ventilation is beyond the scope of this book, some important considerations are as follows:

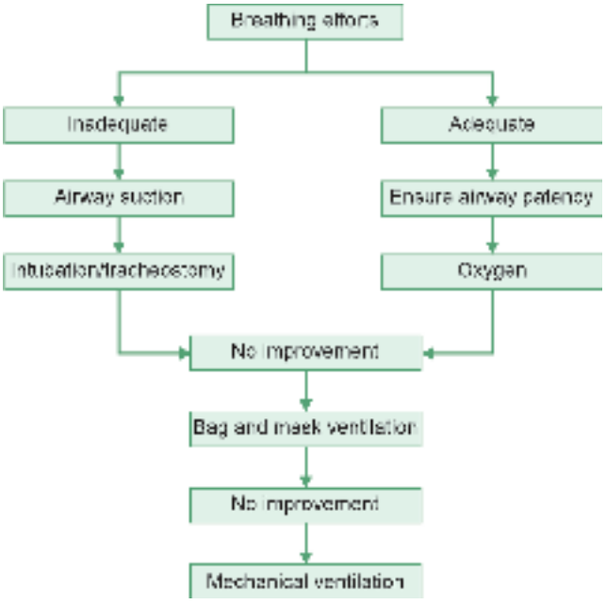


Fig. 27.12: Schematic management plan in ARpF.

TABLE 27.7: Indications for mechanical ventilation

- Prolonged apnea or need for bag and mask ventilation
- $PaCO_2$ > 55 mm Hg
- PaO_2 <60 mm Hg on 60% FiO_2
- Persistent cyanosis on 60% FiO_2
- *Severe acidosis:* pH <7.2

TABLE 27.8: Types of mechanical ventilation

- Controlled mechanical ventilation (CMV)
  - Intermittent positive pressure ventilation (IPPV)
  - Positive end-expiratory pressure ventilation (PEEP)
- Synchronized intermittent mechanical ventilation (SIMV)
- Spontaneous mechanical ventilation, e.g. CPAP
- Newer modalities (see text)

CPAP: Continuous positive airway pressure ventilation

Indications: Mechanical ventilation is indicated in children with persistently poor breathing efforts and deteriorating ABG parameters, despite initial bag and mask ventilation **(Table 27.7)**.

Modes: Primary modes of mechanical ventilation include: (a) *controlled mechanical ventilation (CMV)* in a totally apneic child, (b) *synchronized intermittent mandatory ventilation* (SIMV) in a child with poor breathing efforts, and (c) *spontaneous mechanical ventilation*, e.g. CPAP, in a child with good breathing efforts **(Table 27.8)**. Some newer modes of ventilation are discussed later.

- **Controlled mechanical ventilation** (CMV) may be *volume-cycled* or *pressure-cycled*, the later is preferred due to lesser risk of barotrauma and air-leaks. Two main types of pressure-controlled CMV are: (i) *intermittent positive pressure ventilation* (IPPV), where end-expiratory alveolar pressure falls to zero, and

(ii) *positive end-expiratory pressure ventilation* (PEEP), where a pre-determined positive pressure is maintained even in end-expiration. PEEP is usually used in cases with decreased lung compliance and tendency for alveolar collapse, e.g. hyaline membrane disease or acute respiratory distress syndrome.

- **Spontaneous mechanical ventilation,** e.g. CPAP is used for similar purpose as PEEP, but in a spontaneously breathing child. It may be provided through special ventilator *or* even with an indigenous breathing circuit via endotracheal intubation or long nasal-prongs. CPAP prevents complete collapse of alveoli in end-expiration and thus facilitates longer gaseous exchange and easier re-expansion of lungs during inspiration.
- **Synchronized mechanical ventilation (SIMV)** is used in children with spontaneous but poor respiratory efforts, specially during weaning phase from ventilatory assistance. In SIMV, ventilator allows the child to trigger a breath by spontaneous efforts. However, if patient takes too long time to initiate this effort, the inspiration is triggered by preset inspiration time.

Initial ventilator settings: Although ventilation requirements of each child need to be individualized according to frequently monitored ABG status, initial ventilator settings usually depend on the state of lung compliance and airway resistance **(Table 27.9)**.

For initial setting, the primary pathology may be classified as: (a) normal lung compliance and resistance, (b) decreased lung compliance, e.g. pneumonia, ARDS, atelectasis, pulmonary edema, hyaline membrane disease, etc. and (c) increased airway resistance, e.g. asthma, bronchiolitis, etc.

A higher PEEP with lower inspiratory time is required in disorders with poor lung compliance, while reverse is indicated in cases with high airway resistance.

Monitoring: A child on ventilator should be frequently monitored for clinical improvement/deterioration, air entry into lungs, arterial blood-gases and spontaneous breathing efforts, to determine the need for revision of ventilator settings *or* tracheal tube.

TABLE 27.9: Guidelines for initial ventilator settings

Settings	*Normal*	*↓ compliance*	*↑resistance*
Tidal vol. (ml/kg)	8–12	10–12	10–12
Rate (/min)	Age-wise*	Higher	Lower
PIP (mmH_2O)	20–25	Higher	Higher
PEEP (mmH_2O)	2–4	Higher	Lower
FiO_2	<0.5	<0.6	<0.6
I:E ratio	1:2–1:3	1:1.2	1:3–1.4

*infants: 30, toddlers: 20, older:16.
PIP: Peak inspiratory airway pressure, **PEEP:** Peak end-expiratory pressure, **FiO_2**: Oxygen fraction in inspired air, **I:E ratio:** Inspiratory vs. expiratory time.

Complications: Common complications of assisted mechanical ventilation are: (a) barotrauma, e.g. pneumothorax, (b) nosocomial infections, (c) ventilator malfunction, and (d) tracheal injury, e.g. sub-glottic stenosis.

Newer modes of ventilation: Although not widely available, some important new modes of mechanical ventilation are as follows:

High frequency ventilation (HFV) aims to provide adequate ventilation by increasing the frequency of ventilatory cycles with low tidal volume and inspiratory pressures. It is particularly useful in cases with air-leak syndromes *or* refractory to conventional modes of ventilation.

Heliox ventilation is an experimental mode of ventilation, in which nitrogen in inspired air is substituted with helium. Helium, being an inert gas, facilitates laminar airflow, reduces airway resistance and allows good ventilation at lower inspiratory pressures. It is potentially useful in cases of air-leak syndromes and partial airway obstruction, e.g. croup and asthma.

Nitric oxide (NO) ventilation is based on adding 20–40 ppm of NO in inspired air. As NO is a potent and selective pulmonary capillary vasodilator, it improves ventilation of poorly perfused lung segments and particularly useful in persistent pulmonary hypertension in newborns (PPHN) and acute respiratory distress syndrome (ARDS).

Liquid ventilation, an experimental modality, substitutes air nitrogen with inert perfluorochemical (PFC) liquids, which lower the alveolar surface tension and open atelectatic alveoli for ventilation.

Extra-corporeal membrane oxygenation (ECMO) is an external mode of ventilation, where venous blood is passed through an *in vitro* membrane oxygenator for gaseous exchange (which acts as physiological lung) and then returned back to venous or arterial side. It is a highly effective mode of ventilation, though rarely available and associated with risks of thromboembolic complications and cannulation problems.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is an uncommon but potentially fatal cause of respiratory failure in critically sick children, characterized by:

a. Severe hypoxemia (PaO_2:FiO_2 gradient < 0.2),
b. Diffuse pulmonary infiltrates on chest X-ray,
c. Normal cardiac function.

Etiologically, ARDS is the pulmonary manifestation of systemic inflammatory process, triggered by various events, e.g. viral infections, septicemia, shock, aspiration, head injuries and immunological insults, e.g. bone marrow transplants.

TABLE 27.10: Berlin criteria (2013) for diagnosis of ARDS

- Onset within 1 week of known insult with progression
- Bilateral opacities on chest X-ray resembling pulmonary edema, and not explained by lung pathology[#]
- No obvious cardiac cause or fluid overload
- PaO_2/FiO_2 ratio <300 mm Hg on PEEP/CPAP >5 cm H_2O

Severity classification (PaO_2/FiO_2 Ratio)

*Mild**: 200–300; *Moderate*: 100–200; *Severe*: < 100

[#]*see* **Fig. 16.19**

*Also termed acute lung injury

Pathological course of ARDS may be divided into *three* stages: (i) *Exudative phase* with increased capillary permeability leading to alveolar exudation (2–3 days), (ii) *Proliferative phase* with fibroblast proliferation (2–3 weeks), and (iii) *pulmonary fibrosis* in survivors with decreased lung compliance and vital capacity.

Clinically, early cases present like any other pneumonia, but with progressive hypoxia and hypercarbia, which does not respond to regular therapy.

Possibility of ARDS should be considered in any critically sick child, when SaO_2 fails to rise >92% on >50% FiO_2 delivered via spontaneous or assisted ventilation.

Diagnosis of ARDS should be considered in any case of pulmonary edema on chest skiagram **(Fig. 16.19)** without cardiac etiology, and confirmed on PaO_2/FiO_2 ratio, along with exclusion of other causes. *Berlin criteria* (2013) is commonly used to diagnose and classify the severity. **(Table 27.10)**.

Management of these cases revolves around high *PEEP ventilation* for expansion of exudates-filled alveoli and reduce intrapulmonary shunting. Other modes of ventilation, e.g. high-frequency ventilation *or* extracorporeal membrane oxygenation (ECMO) are necessary in cases with high PEEP (>15 cm H_2O) requirements and risk of air-leak syndromes.

Outcome is poor in most cases, with overall mortality ranging from 40–60% in early diagnosed cases to ~ 100% in un-ventilated cases.

27.3 SHOCK

The term 'Shock' denotes a *"clinico-pathological state of circulatory insufficiency to meet metabolic and oxygen demand of tissues, due to any cause'*. While hypotension is a common preceding event, shock may also develop despite well-maintained blood pressure due to inappropriate micro-circulation, e.g. compensated shock.

Etiology: Adequate tissue perfusion depends on four major and interdependent factors: (a) blood volume, (b) myocardial function, (c) A-V pressure gradient at tissue level that determines capillary flow velocity and time available for exchange of oxygen/metabolites, and (d) integrity of microvascular capillary bed.

TABLE 27.11: Causes of circulatory shock

- **Hypovolemic shock**
  - *External fluid losses:*
    - *GIT:* Diarrhea, vomiting
    - *Urinary:* Diabetes insipidus
    - *Skin:* Heat stroke, burns
    - *Lungs:* Severe respiratory distress
  - *3rd space losses:* Ascites, paralytic ileus, edema
  - *Blood loss:* Trauma, surgery, GI bleeding
- **Septic shock**
- **Distributive**
  - *Anaphylaxis:* Drugs, envenomation
  - *Neurogenic:* Head injury, spinal shock
  - *Toxic*
- **Cardiogenic shock**
  - *Primary:* Myocarditis, myocardiopathy
  - *Secondary:* CCF, CHDs, RHDs
- **Obstructive shock**
  - *Cardiac:* Pericardial tamponade, aortic stenosis
  - *Vascular:* Coarctation of aorta
  - *Lungs:* Tension pneumothorax, severe asthma

Shock represents abnormality in any one *or* more of these factors due to any cause. Consequently, it may be classified as **(Table 27.11)**:

a. ***Hypovolemic shock,*** due to decreased intravascular volume, e.g. dehydration;
b. ***Distributive shock,*** due to decreased vascular tone with vasodilatation, increased venous capacitance and hypovolemia, e.g. anaphylaxis or septic shock;
c. ***Cardiogenic shock,*** due to impaired myocardial contractility, e.g. myocarditis;
d. ***Obstructive shock*** due to reduced cardiac output despite adequate myocardial contractility, e.g. pericardial tamponade;
e. ***Dissociative shock,*** due to impaired oxygen utilization by cells, despite normal perfusion, e.g. abnormal Hb, preventing release of oxygen in tissues.

Septic shock, commonly seen in gram-negative infections, is a unique combination of distributive, hypovolemic, and cardiogenic shock, due to peripheral vasodilatation, capillary leak and myocardial dysfunction respectively. Apart from the infection *per se*, endogenous release of inflammatory mediators in response to the infection (*Systemic inflammatory response syndrome or SIRS)* contributes to the pathophysiology of septic shock.

In children, hypovolemic shock and septic shock are two most common causes of shock.

Pathophysiology of shock may be broadly divided in three stages—(a) compensated shock, (b) uncompensated or decompensated shock, and (c) multi-organ dysfunction.

Impaired tissue perfusion is the pathophysiological hallmark of shock that triggers various compensatory mechanisms to restore blood flow to vital organs, e.g. increase in HR, stroke volume, vascular tone and respiration (***compensated shock***). However, failure

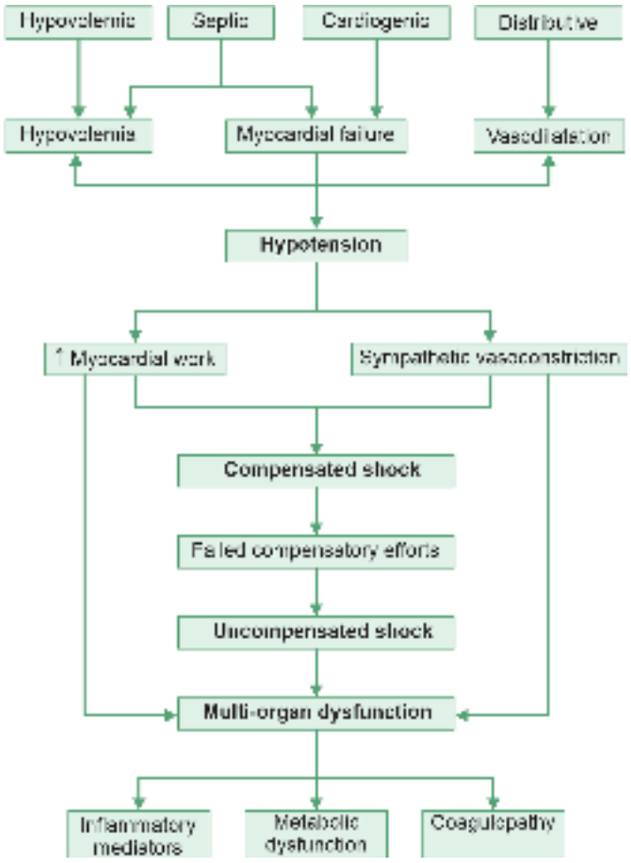


Fig. 27.13: Pathogenesis of shock.

of these compensatory mechanisms (***uncompensated shock***) leads to cellular hypoperfusion > hypoxia > shift to anaerobic metabolism > acidosis and ultimately ***multiorgan dysfunction***, e.g. renal failure, hypoxic-ischemic brain damage, myocardial failure, acute respiratory distress syndrome (ARDS), hepatic failure, metabolic derangements, DIC and death **(Fig. 27.13)**.

The term ***cold shock*** is used to denote shock with decreased capillary refill (>3 seconds), which is normal (<3 seconds) in ***warm shock***.

Diagnosis: Early diagnosis of shock in compensated state and its etiology is vital to prevent irreversible multi-organ dysfunction. Assessment of a child in shock includes:

a. ***Detailed history***, regarding *etiology*, e.g. fluid/blood loss, drug/toxin exposure, fever, previous cardiac disease, etc. as well as state of *organ functions*, e.g. urine output, sensorium, respiratory distress, etc.

b. ***Clinical examination***, to differentiate between compensated and uncompensated shock **(Table 27.12)**, to identify possible etiology, and to assess organ damage. While tachycardia is the first compensatory phenomena, two other reliable signs of early/compensated shock are: (i) *increased capillary filling time* (>3 second), usually tested on the heels by blanching, and (ii) *increased core (rectal) vs peripheral temperature gradient* (>2°C). BP may be normal in compensated state, though pulse pressure falls earlier, due to decreased systolic pressure.

TABLE 27.12: Clinical signs of shock

	Compensated	*Uncompensated*
Heart rate	Tachycardia	Bradycardia
Pulses	↓ Capillary refill	Absent
BP	↓ Pulse pressure	Hypotension
Respiration	Tachypnea	Gasping
Temperature	C:P gradient* >2	Hypothermia
Extremities	Cold**, clammy	Pale/cyanosed
Urine output	Oliguria	Oliguria/anuria
Mental status	Drowsiness	Altered, coma

*Core (rectal)-Peripheral (axillary) temperature difference of >2°C
**Warm extremities indicate septic shock

c. ***Investigations*** in shock are usually deferred till initial stabilization, when detailed work-up is necessary for etiological diagnosis as well as to assess exact hemodynamic status and organ dysfunction. Important baseline investigations include:

- *Hematological work-up* for
  - Hemoglobin (need for transfusion)
  - White cell counts (septic etiology)
  - Coagulation profile (secondary coagulopathy)
- *Biochemical work-up*, for
  - Arterial blood gases (metabolic acidosis)
  - Serum electrolytes
  - Renal/liver function tests (organ dysfunction)
  - Blood sugar (hypoglycemia)
- Chest X-ray (for ARDS, i.e. *shock-lung*)
- Other relevant investigations, as required for etiological diagnosis.

Management of shock aims to—(a) restore adequate perfusion, (b) revert secondary organ damage, and (c) treat the primary cause. Important steps in management of shock are as follows:

Step I. Quick clinical assessment regarding presence of shock, its severity and probable cause, as well as general cardiopulmonary status and need for resuscitation.

Step II. Initial cardiopulmonary stabilization, i.e. ensuring airway patency and breathing support with 100% oxygen and/or assisted ventilation. Child should be placed in *Trendelenburg position* (supine with elevated legs) to facilitate cerebral perfusion.

Step III. Vascular access should be obtained as early as possible, via cannulation of a peripheral vein, or a large central vein, e.g. femoral or internal jugular vein. *Intraosseous route* may be effectively utilized in younger children with difficult venous access for immediate volume correction (*see* Ch 32.3).

TABLE 27.13: Inotropic/vasopressor therapy in shock

Drugs	*Dose (µg/kg/min)*	*Mode of action*
Dopamine	10-20	Inotrope + vasoconstrictor*
Dobutamine	10-20	Inotrope + Vasodilator
Epinephrine	0.1-2**	Inotrope + vasoconstrictor
Norepinephrine	0.1-1	Vasoconstrictor
Amrinone	5-10***	Inotrope + Vasodilator
Milrinone	0.3-0.7	Inotrope + Vasodilator

**Improves / preserves Renal blood flow in doses <10 µg/kg/min*
*** vasoconstrictor in doses > 2 µg/kg/min*
**** Load with 1.5-5 mg/kg bolus over 20 minutes*

Step IV. Immediate volume expansion with 20 ml/kg of isotonic crystalloid infusion, e.g. Ringer lactate or Normal saline, over a period of 10–15 minutes is indicated in all cases, irrespective of the etiology of shock or hemodynamic status. Similar infusions may be repeated 2–3 times (max 60 ml/kg) over next one hour, if BP remains unrecordable *or* clinical improvement is not obvious. Colloids *or* blood transfusions have no role in immediate volume expansion.

Step V. Vasoactive agents, to improve myocardial function as well as to modify peripheral vascular resistance are indicated in—(a) hypovolemic shock not responding to volume expansion, *or* (b) all cases of nonhypovolemic, e.g. cardiogenic or septic shock. Many inotropic and vasopressor agents are available **(Table 27.13)** with variable effects on peripheral vascular resistance and the choice depends on cause of shock and hemodynamic status.

Generally, *Dopamine* (10 µg/kg/minutes) is preferred in most cases, for its beneficial vasodilator action on renal/splanchnic circulation along with inotropic effect at lower doses. Infusion rate must be titrated to response, up to 20 µg/kg/min.

Dobutamine-a pure inotropic agent with negligible peripheral effects is preferred in cardiogenic shock to augment myocardial contractility.

Norepinephrine is the inotrope of choice in septic and anaphylactic shock (with peripheral vasodilation), due to its peripheral vasoconstrictor effect.

Phosphodiesterase inhibitors, e.g. Amrinone or Milrinone, improve myocardial function directly by facilitating intracellular cAMP synthesis. However, these agents are potent peripheral vasodilators and should be used only after adequate volume replacement.

Selective vasodilators, e.g. sodium nitroprusside, (IV 0.3–7 µg/kg/minute) though rarely used, may be useful in selected cases of cardiogenic shock to reduce afterload and improve cardiac output during recovery phase.

Step VI. Reassessment of hemodynamic status is indicated as soon as BP starts improving and patient is stabilized with above measures. Most important concern at this stage is to avoid fluid overload and myocardial strain. Hence, it is preferable to establish a central venous line for monitoring of central venous pressure (CVP). Relevant investigations for etiological diagnosis are also indicated at this stage. Basic monitoring parameters in shock include:

- *Clinical signs*, e.g. HR, RR, BP, temperature and sensorium;
- *Hemodynamic monitoring* with CVP, PAWP;
- *Respiratory monitoring* with pulse oximetry and periodic ABG analysis; and
- *Metabolic monitoring* for electrolyte status.

CVP monitoring involves placement of a long venous catheter into right atrium through a peripheral vein. CVP is a very useful indicator of venous return and cardiac preload in hypotension/shock. Low CVP (<10 cm water) in shock indicates need for further fluid replacement while high CVP warns about the risk of volume overload or compromised myocardial function, to be managed with inotropic agents.

Pulmonary airway wedge pressures (PAWP), though more reliable indicator of circulatory overload, are difficult to monitor in day-to-day practice.

Step VII. Controlled fluid replacement, after initial volume expansion aims to keep: (a) BP >5th percentile, and (b) CVP between 10 and 16 cm H_2O; and the rate of infusion should be guided with these parameters. Colloidal solutions, e.g. albumin, may be used at this stage, though blood is the best colloidal agent and also increases O_2 carrying capacity. Blood transfusion is indicated in cases of hemorrhagic shock or severe anemia.

Step VIII. Other Supportive measures should also be instituted after initial hemodynamic stabilization, including: (i) adequate nutrition, (ii) antibiotics, (iii) correction of metabolic abnormalities, e.g. hypoglycemia, acidosis and dyselectrolytemia.

Role of steroids, except in anaphylactic shock or adrenal crisis, is highly controversial, generally not indicated. Extracorporeal membrane perfusion and intra-aortic balloon pulsations are recent methods to maintain normal circulation in refractory cases of shock.

Step IX. Management of multi-organ dysfunction, discussed below, is usually a terminal event in shock, with wide clinical spectrum and high mortality. All cases of shock should be constantly monitored for early diagnosis of various organ dysfunctions and necessary support.

Figure 27.14 provides an algorithm to manage septic shock - the trickiest of all types due to combination of distributive, hypovolemic and cardiogenic factors, with high mortality.

Multi-organ Dysfunction Syndrome

Multiple organ dysfunction syndrome (MODS) denotes a constellation of common terminal events in critically sick children. It is defined as a state of "*altered organ*

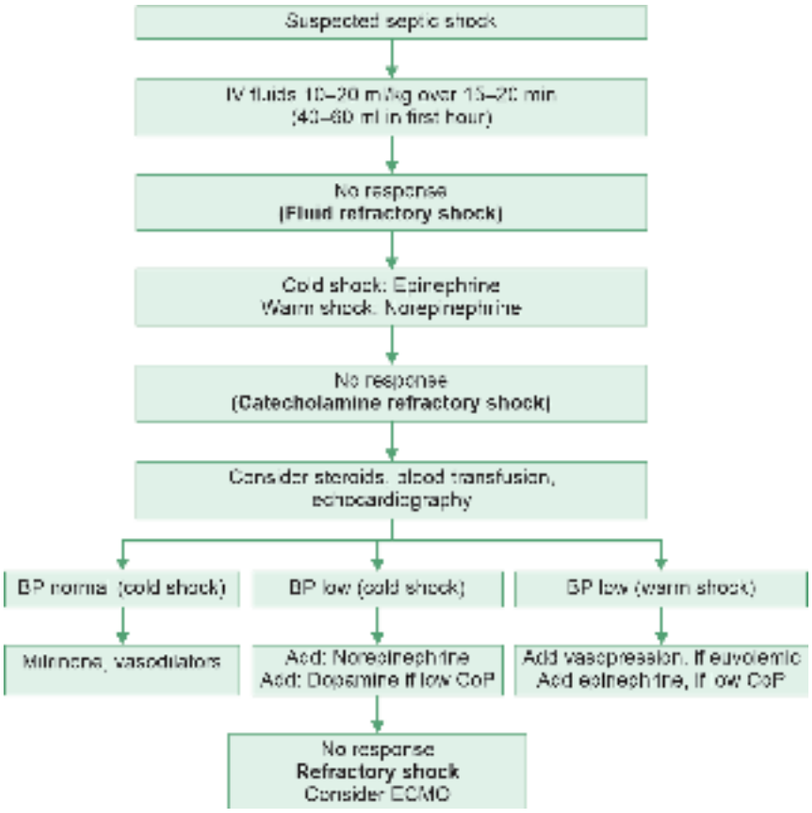


Fig. 27.14: Management of septic shock.

function in an acutely ill patient so that homeostasis cannot be maintained without intervention."

MODS may be classified as: (a) *primary*, i.e. direct insult to multiple organs due to exogenous factors, e.g. bacteria or toxins, and (b) *secondary, i.e. a* consequence of exaggerated host response with generalized activation of inflammatory reactions in organs remote to the site of initial insult.

Pathogenesis: Though exact pathogenesis is unclear, important contributory factors for MODS include:

- Excessive stimulation of macrophages and consequent release of many humoral and chemical mediators, e.g. cytokines, (e.g. TNFα, IL-1, IL-6, etc.), bradykinin, nitric oxide, etc.
- Ischemic perfusion injury to vascular endothelium with consequent congestion, sludging and microthrombi formation.
- Impaired intestinal barrier, permitting entry of pathogenic gut organisms and endotoxins into systemic circulation.
- Generalized tissue hypoxia and consequent impairment of clearance mechanisms.

Clinical course: Regardless of etiology, MODS follows a downhill course in a critically sick child. Important manifestations include:

- *Lungs :* Acute respiratory distress syndrome.
- *GIT :* Bleeding, diarrhea, paralytic ileus.
- *CVS :* Shock or CCF.
- *Renal :* Oliguria and acute renal failure.
- *CNS :* Altered sensorium, seizures, encephalopathy.
- *Blood :* Bleeding diathesis, DIC, marrow failure.

Hepatic encephalopathy is relatively uncommon in children than in adults.

Management: Prompt recognition and treatment of potential causes is the most effective strategy in management of MODS, which includes: (a) appropriate antibiotic therapy, (b) local measures, e.g. drainage of abscesses, etc., (c) adequate hemodynamic and ventilatory support, and (d) continuous monitoring of various organ functions in intensive care unit.

Important diagnostic indicators as well as therapeutic interventions for various components of MODS are given in **Table 27.14**.

TABLE 27.14: Management of MODS in shock

Complication (Criteria)	*Management*
ARDS (SaO_2 <92% at 50% FiO_2)	Mech. ventilation (PEEP)
Ac renal failure (S. creatinine >2)	Dopamine, dialysis
DIC (FDP >40 dimers)	Transfusion, ? heparin
Encephalopathy (GCS* <15)	ICP monitoring, steroids
Liver dysfunction (SGOT/PT**)	Fluid/electrolyte correction

*Glasgow coma scale
**More than two times of normal

27.4 PEDIATRIC INTENSIVE CARE

Pediatric intensive care unit (PICU) is an integral part of tertiary pediatric care centers, essential for advanced life support (PALS) and care of critically sick children. While some components of PALS, e.g. diagnosis and treatment of respiratory failure or circulatory shock, have been discussed in earlier chapters, this chapter deals with other important issues in pediatric intensive care.

27.4.1 CONSENSUS GUIDELINES FOR PICU

While detailed discussion on this set-up is beyond the scope of this book, some important aspects are discussed here:

- ***Size:*** PICU should constitute at least ~15% of total bed strength in pediatric ward of a referral center, as per National medical commission guidelines.
- ***Area:*** Each PICU bed should have ~200 sq. feet of area, along with adequate space for placement and storage of equipment, emergency movements of medical personnel and central monitoring station. Generally, the total area of PICU should be three times of the size calculated for beds alone.
- ***Staff:*** Each PICU should be supervised by a trained intensivist, supported by round the clock availability of trained medical/paramedical personal. The ideal Nurse-patient ratio for PICU is 1:1, with a minimum of 1:3.
- ***Equipment:*** Each PICU should be equipped with enough numbers of state-of-art monitoring, resuscitation and treatment-delivery equipments, as well as round-the-clock facility for laboratory and radiological investigations.
- ***Admission/discharge protocol*:** In order to optimize resource utilization, each IPCU should have a written standard admission as well as discharge/transfer criteria, discussed later.
- ***Treatment protocols*:** Although each patient in PICU presents with unique problems, it is advisable to have written standard management protocols for common problems in intensive care to assist quick and rational decision-making by on-site staff.
- ***Infection control policy*:** Nosocomial infections are major killers in PICU set-ups. Each PICU should have a written infection-control policy, with special reference to hand washing, cleaning/sterilization procedures and antibiotic usage.

27.4.2 ADMISSION CRITERIA FOR PICU

Intensive care is a highly specialized and costly service that cannot be provided to each and every sick child. For maximum cost-effective utilization, it is essential to ensure that only critically sick children, who need constant monitoring and advanced therapeutic interventions are admitted in PICUs. Depending on the needs and facilities, two levels of PICUs have been identified: Level II and III in order of increasing facilities, which should be located near the regular wards. A *'step-up and step-down'* approach may be used between these two levels and general wards, depending on the individual needs of patients. Some common indications for PICU care are given in **Table 27.15**.

TABLE 27.15: Admission criteria for PICUs

Level III care

- Patients who need invasive monitoring*
- Patients, who have recently recovered after CPR
- *Patients with:*
  - Respiratory failure, requiring mechanical ventilation
  - Circulatory shock, arrhythmia, hypertensive crisis
  - *Acute neurological insult:* Coma, status epilepticus
  - Acute renal failure, requiring dialysis
  - Acute bleeding disorders, requiring transfusions
- *Post-operative cases:* Unstable or on life-support

Level II care

- Patients, who need close but non-invasive monitoring
- *Patients with:*
  - Severe respiratory distress on oxygen, tracheostomy, etc. (not on mechanical ventilation)
  - Impending cardiovascular insufficiency
  - Acute neurological injury with patent airway
  - Stable cases of single/multi-organ failure (MODS)
- Accident/poisoning victims for observation
- Stable post-operative cases after major surgeries
- Step-down patients from level III care

*CVP lines, ICP catheters etc.

27.4.3 VASCULAR ACCESS IN SICK CHILDREN

A reliable venous access is the crucial step in PALS and intensive care, though temporary intraosseous access (discussed later) may be used for emergency fluid and drug administration, if a reliable venous access cannot be achieved within three attempts *or* 90 seconds. Two common approaches to venous access in sick children in PICU are—(a) peripheral venous cannulation, and (b) central venous cannulation, with procedural details provided in Ch 31.3. Intraosseous cannulation is another short-term option in emergency, while venesection is no longer used routinely.

Peripheral venous cannulation (PVC) is easier and preferred choice for venous access, though with higher risks of—(a) displacement, (b) local extravasation, thrombophlebitis, cellulitis or gangrene, (c) catheter-related infections, and rarely (d) air or catheter-fragment embolism. Potential risk of infections increases after 48-72 hours, requiring change of location even if no displacement.

Central venous cannulation (CVC) that reaches up to superior vena cava *or* right atrium is used in intensive care for—(a) hemodynamic (e.g. CVP) monitoring, (b) frequent blood collections, and (c) prolonged infusion

of irritating solutions, e.g. total parenteral nutrition. However, CVC carries higher risk of complications, e.g. infections, thromboembolism, traumatic bleeding and arrhythmia.

Intraosseous cannulation is a safe, simple and reliable method to administer drugs and fluids in emergency, when IV access is difficult and cannot be achieved within three attempts or 90 seconds. This access can be easily obtained in children < 6 years and any IV fluids or drugs may be infused via intraosseous route with comparable dose, onset of action and efficacy. However, rapid volume infusions or viscous drugs may need to be administered under pressure to overcome resistance of emissary veins (*see* Ch 32.3) Complications are rare (<1%) but tends to be more severe than PVC and hence, this procedure should be reserved only as a temporary measure till suitable venous access is obtained. Potential complications include—(a) tibial fracture, (b) local skin necrosis or compartment syndrome, (c) osteomyelitis and very rarely, (d) fat embolism.

27.4.4 MONITORING OF CRITICALLY SICK CHILD

Continuous monitoring is an essential component of care for a critically sick child in PICU, which includes periodic clinical and laboratory assessment of physiological parameters, as well as real-time monitoring with electronic equipments.

Although all systems deserve close monitoring in a sick child, five major areas of concern are—(a) hemodynamic imbalance, (b) respiratory insufficiency, (c) neurological damage, (d) renal damage, *and* (e) metabolic or electrolyte disturbances.

A. Respiratory monitoring aims to assess the state of gaseous exchange in lungs and includes: (a) *clinical* monitoring of respiratory rate, depth, efforts, cyanosis and air entry on auscultation, (b) periodic *arterial blood gas analysis (Ch 7.6),* and (c) *non-invasive monitoring* of ventilatory functions, e.g. pulse oximetry or capnography.

Pulse oximetry is a simple non-invasive method to monitor percentage of hemoglobin saturated with oxygen (SaO_2), with an accuracy of + 2%. However, Pulse oximeters are unreliable once the SaO_2 drops >70%. False values may also be obtained due to: (a) low capillary perfusion, e.g. shock, (b) presence of abnormal hemoglobin, e.g. methemoglobin or carboxyhemoglobin, (c) optic interference with external light source, e.g. phototherapy or warmers.

Capnography is a non-invasive method to monitor CO_2 changes in expired air during critical care or anesthesia, as a measure of—(a) altered CO_2 production, (b) altered pulmonary perfusion or cardiac output, (c) altered ventilatory system. It is continuously measured by an optical beach connected to patient's airway via T-tube and expressed as a wave-form on digital monitor. Important $EtCO_2$ abnormalities are:

- *Sudden drop* in $EtCO_2$ indicates airway block, ventilator malfunction/extubation or pulmonary hypoperfusion, e.g. shock or pulmonary embolism,
- *Slow and sustained drop* indicates combined cardio-respiratory failure.
- *Sudden, exponential rise* in $EtCO_2$ indicates acute delivery of CO_2 in pulmonary circulation, e.g. bicarbonate injection,
- *Gradual rise* in $EtCO_2$ indicates alveolar hypoventilation or partial airway obstruction

B. Hemodynamic monitoring aims to assess the state of circulatory sufficiency at tissue levels and includes-(a) *clinical* monitoring of heart rate and rhythm, pulse volume, capillary filling time and blood pressure, (b) invasive *central venous pressure* monitoring (Ch 27.3), and (c) *non-invasive* BP monitoring.

Non-invasive BP monitoring **(NIBP)** is the standard of care in PICUs, which may be periodic or continuous.

Periodic NIBP involves use of automated oscillometric method, using a special double air-bladder cuff, tied over a peripheral artery. Proximal bladder is periodically inflated to occlude arterial flow, while distal one records oscillations during cardiac cycle and transmits them as digital signals to depict systolic, diastolic and mean BP.

Continuous NIBP is based on the principle of "force balance technology", i.e. the force exerted by systolic BP and the counter force required to counteract it. A finger cuff/probe is inflated and deflated in rapid sequence automatically via a servo system, while a light-emitting electrode on one clip transilluminates the capillary bed. Photo-iodide cell on the opposite clip measures the change in light intensity during various phases of cardiac cycle and produces equal counteracting pressure to occlude it, which is measured digitally.

C. Neurological monitoring is critically sick children generally include frequent clinical assessment of: (a) level of sensorium, (b) pupillary responses, (c) signs of raised intracranial pressure, apart from periodic evaluation of motor and other neurological signs. *Glasgow coma scale* is commonly used to monitor the level of sensorium in critically sick children (Ch 18.3).

D. Renal monitoring involves: (a) clinical assessment of urinary output for oliguria, and (b) periodic renal function tests, e.g. blood urea nitrogen, serum creatinine, etc. Urine output of <0.5 ml/kg/hour indicates poor renal perfusion, intrinsic renal dysfunction *or* excess ADH secretion (SIADH) that needs modifications in fluid therapy.

E. Metabolic monitoring is the most crucial component of monitoring in critically sick children after hemodynamic and respiratory assessments. Some extent of metabolic derangements due to endogenous events *or* exogenous

fluid/electrolyte/drug therapy is inevitable in most children under PICU care, which need careful correction. Common parameters for metabolic monitoring include: (a) blood glucose, (b) serum electrolytes, e.g. Na^+, K^+ and Ca^{++}, (c) acid-base status (Ch 7.6), (d) serum lactate and ammonia levels, apart from renal/hepatic function tests.

27.4.5 NUTRITION IN CRITICALLY SICK CHILD

Critically sick children are in hyper-catabolic state and need additional nutrition to maintain their nitrogen balance. Conventional fluid and electrolyte supplementation with simple dextrose-solutions is grossly inadequate to meet nutritional requirements of these children except for brief periods.

Nutritional requirements of a critically sick child are actually higher than those of a normal child *but* complete supplementation is often difficult. However, these children should at least receive *~25–30 cal/kg/day* (~40–45 cal/kg/day in burns or trauma) and *1.5–2.5 gm/day of proteins* (2.5–3.0 gm/day in burns), via enteral *or* parenteral route, which should be increased gradually.

Enteral feeding is the preferred route of nutrition in sick children, which prevents intestinal mucosal damage and overgrowth of gut pathogens in critically sick children. However, it is contraindicated in many situations, e.g. paralytic ileus, gut perforation or gut hemorrhage.

Enteral feeding may be given *via* nasogastric tube intermittently *or* as continuous intragastric/small bowel drip. Milk *or* milk-based feeds are preferred enteral feeds in sick children, while commercially available oligomeric diets, e.g. glucose polymers, free aminoacid preparations, medium chain triglycerides, etc. may be necessary in selected cases. Bolus feeds are preferred than continuous feeding, unless transpyloric feeding is required.

Enteral feeding is contraindicated in intestinal obstruction, severe GIT bleeding and recent GIT surgery. Common complications of prolonged enteral feeding include: (a) aspiration due to displaced nasogastric tube, (b) diarrhea due to hyperosmolar feeds, and (c) local nasopharyngeal trauma.

Total parenteral nutrition (TPN) aims to provide all essential nutrients, e.g. proteins, fats, carbohydrates, vitamins and trace elements via parenteral route, when enteral nutrition is not possible for longer periods (>7 days). It is a highly specialized intervention that needs close supervision by experienced staff as well as adequate laboratory support.

Indications: Common indications for TPN are given in **Table 27.16**.

TABLE 27.16: Indications for TPN

Newborns:
- Very low birth weight newborns
- Prolonged resp. distress or mechanical ventilation
- Gut malformations or necrotizing enterocolitis
- Post-operative GIT surgery

Older children
- Gut malformations, e.g. short gut syndrome
- Persistent diarrhea or paralytic ileus
- Chronic liver/renal failure
- Severe trauma or burns

Preparations: Various IV commercial preparations are available for TPN, which include:

- *Lipids* preparations, containing 10–20% of emulsified Soyaben *or* Safflower oil, should be started with 0.5 gm/kg/day and increased gradually to reach 2 gm/kg/day within a week.
- *Amino acids* mixtures, containing at least 40% as essential amino acids, should be started with 1.0 gm/kg/day and increased gradually to 1.5–2.0 gm/kg/day.
- *Carbohydrates* as 10% dextrose infusion provide remaining caloric requirements, which should begin with 5–6 mg/kg/minutes before increasing gradually.
- *Microelements*, e.g. vitamins, mineral and electrolytes, must be added in IV fluids as per daily requirements.

Mode: Peripheral venous lines are preferred for TPN due to higher risk of complications with central catheters, which should be used only when high dextrose concentration (>10%) is necessary to meet caloric demands. TPN should be introduced gradually over a period of 2–4 days. Amino acids, dextrose and electrolytes can be mixed in the same bottle under asepsis, while lipids have to be administered by separate IV lines. Enteral feeding should be started as soon as possible and TPN can be stopped when >3/4th requirement may be given enterally/orally.

Monitoring: All patients on TPN should be monitored for blood glucose thrice a day, apart from daily weight record and periodic serum electrolytes, BUN, triglycerides and complete blood counts for infection.

Complications of TPN are directly related to duration of therapy as well as quality of care, and include:

- *Local* thrombophlebitis, extravasation gangrene.
- *Infections:* Local abscess, septicemia
- *Metabolic:* Dyselectrolytemia, acidosis, hyperglycemia, hypertriglyceridemia.
- *Thromboembolic:* Pulmonary, air *or* lipid embolism
- Systemic *bleeding diathesis*
- *Mechanical* vascular/thoracic duct injury
- *Late complications:* Cholestatic liver dysfunction and essential fatty acid deficiency.

27.4.6 SEDATION AND ANALGESIA IN INTENSIVE CARE

Sedation is frequently needed in PICUs to provide analgesia, control unwanted motions and reduce the anxiety related to either primary disease or various procedures and interventions.

TABLE 27.17: Common drugs for sedation and analgesia

Drug	*Dose*	*Onset/duration*
A: Drugs for sedation without analgesia		
Triclofos	PO 20–100 mg/kg	30 min/4 hr
Chloral hydrate	PO 25–100 mg/kg	15 min/2 hr
Midazolam	IV 0.1–0.4 mg/kg*	2 min/60 min
Diazepam	IV 0.2–0.3 mg/kg	2 min/2 hr
Propofol	IV 5–10 mg/kg/hr	1 min/10 min
B: Drugs for sedation with analgesia		
Fentanyl	IV 1–5 µg/kg/hr*	2 min/40 min
Ketamine	IV 1–1.5 mg/kg	3 min/60 min
Morphine	IV 0.1 mg/kg	3min/6 hr

*Or continuous IV infusion 0.5 µg/kg/hr

TABLE 27.18: PRISM scoring

Vital signs
- Systolic BP
- Heart rate
- Stupor/coma (GCS <8)
- Pupillary reflexes

Acid–base status
- PH <7.28 or > 7.48
- Total CO_2 >34 mmol/L
- PaO_2 <50 mm Hg
- $PaCO_2$ >50 mm Hg

Blood chemistry
- Blood sugar (>200 mg/dl)
- S. potassium (>6.9 mmol/L)
- Elevated S. creatinine
- Elevated blood urea

Hematology
- TLC < 3000 cells/mm^3
- Platelet count <50,000/mm^3
- PT (>22 sec)/PTT (>57 sec)

Others:
- Non-operative illness
- Chromosomal anomaly
- Cancer
- Previous PICU admission
- Pre-ICU resuscitation
- Post-operative stage
- Diabetes (Ketoacidosis)
- Transfer from inpatient unit

GCS: Glasgow coma scale

Sedation is frequently required to:
- To avoid sudden movements and minimize anxiety during various non-invasive procedures, e.g. USG/CT/MRI, ECG/EEG/ECHO, etc.
- To minimize anxiety and pain during common procedures, e.g. intravenous cannulations and blood collections.
- To minimize substantial pain associated with invasive procedures, e.g. biopsies, tappings, aspiration cytologies and abscess drainage procedures.
- To avoid unexpected respiratory movements in a ventilated child

However, the depth and duration of sedation has to be appropriate to the needs and should not compromise vital functions. **Table 27.17)** provides commonly used drugs for sedation and analgesia in children, some of which can be given as continuous infusions till needed.

27.4.7 PREDICTION OF OUTCOME (PRISM SCORE)

PRISM score (*P*ediatric *Ris*k of *M*ortality) is a commonly used scoring system in PICUs to evaluate the efficacy of care and compare it with others.

Based on 17 physiological variables, PRISM score has demonstrated consistent relationship between the score at 12 and 24 hours and the mortality risk in a given PICU **(Table 27.18)**. However, it is of limited predictive value in an individual case.

Many other scores, e.g. Pediatric Index of mortality (PIM1,2 and 3) are also available to predict outcome of patients admitted in PICU.

27.4.8 COUNSELING PARENTS OF SERIOUS/ TERMINALLY ILL CHILD

Breaking the bad news to parents about their children, is a very difficult task, which should be handled with care. While many protocols, e.g. *Spikes protocol*, have been suggested for this purpose, basic considerations are as follows:
- Prepare in advance about what and how much information must be conveyed?
- Ensure privacy and confidentiality. It is better to have a dedicated counseling room for this purpose.
- Assess the level of understanding and expectation of the parents/relatives.
- Use simple language for honest communication, being sensitive and careful to the nonverbal language/clues.
- Provide the realistic assessment and avoid false reassurances.
- Allow enough time for parents/relatives to assimilate the information and respect their emotions
- Offers them alternative options and respect their choices.
- Document the counseling session, though audio/video-recording is usually not necessary.

27.4.9 DEATH CRITERIA AND BRAIN DEATH

The issue that '*when to declare a PICU baby dead*' is highly complex with ethical and medicolegal dimensions. Death is defined as permanent cessation of *organism as a whole* (and not *of the whole organism*, i.e. does not require cessation of function of every neuron).

Brain death denotes irreversible cessation of all functions of the entire brain, including the brainstem with no chances of revival and survival without external support. The concept of the Brain death is important for the purpose of organ retrieval in cadaveric donations and organ transplant. In children, brain death usually occurs following traumatic brain injury and asphyxia.

Criteria: Brain death is primarily a clinical diagnosis based on at least two evaluations at least 24-hours apart, preferably supported by flat isoelectrical EEG or other

TABLE 27.19: Criteria for brain death*

(All of the following for >24 hours)

- **Presence of definite coma**
  - No spontaneous movements or communication
  - No response to external, even noxious, stimuli**
  - No decerebrate or decorticate posture
- **Absence of brain-stem reflexes, e.g.**
  - Fixed dilated pupils
  - No oculocephalic, vestibular, corneal, gag reflex
- **Positive apnea test**
- **Flat or isolectric EEG**
- **Absence of reversible causes,** e.g. drugs, toxins, shock, etc.

*Based on American Academy of Pediatrics, et al. Guidelines 2011.
**Presence of spinal reflexes do not preclude diagnosis of brain death.

ancillary tests **(Table 27.19)**. Potentially reversible causes of coma, e.g. metabolic disorders, drugs and toxins, hypothermia, hypoxia, shock, etc. must be excluded.

Apnea test is used to confirm the inability of the medulla to drive ventilation in cases of brain death, i.e. absence of respiratory efforts despite controlled stimulus, i.e. critical hypercarbia.

Considering the potential risk of destabilizing the patient, apnea test must be performed only if the first two criteria for brain death (irreversible coma and absence of brain-stem reflexes) are fulfilled, along with—(a) core temperature >35°C, (b) normal blood pressure, (c) not on sedatives or neuromuscular blocking medications, (d) absence of severe electrolyte, blood gas or metabolic abnormalities.

For this test, patient is first ventilated with 100% oxygen to achieve a pCO_2 of ~40 mm Hg on baseline blood gas analysis. Subsequently, ventilatory support is withdrawn and blood gas analysis is repeated every 5 minutes until the target pCO_2 is surpassed. *Absence of respiratory efforts even after pCO_2 has crossed >60 mm Hg or >20 mm Hg above baseline, indicates positive apnea test.* Patient should be closely monitored during the test for hemodynamic status and oxygen saturation and the test should be aborted, if patient becomes hypoxic or hypotensive.

According to Indian *human organ transplant act 2014*, *two apnea tests are required at minimum 6 hours interval* to declare brain death. Some ancillary tests, e.g. EEG, transcranial Doppler USG in young infants and cerebral angiography may also be required in infants <1 year.

Following a diagnosis of brain death, supportive care must continue till the family accepts it and makes final decision about potential organ donation.

27.5 ACCIDENTS IN CHILDHOOD

Accidents account for ~10–15% of total pediatric admissions in Indian hospitals. Common childhood accidents include: (a) physical trauma *or* injuries, (b) burns, (c) drowning, (d) poisonings, and (e) foreign body inhalation *or* ingestion. In addition, envenomations, e.g. snake bite or scorpion sting, etc. and heat or cold injuries are common in certain geographical locations. This chapter deals with some common accidents in childhood, excluding poisonings, which have been discussed in next chapter.

27.5.1 CHILDHOOD TRAUMA

Trauma, accidental *or* intentional, is the leading cause of childhood deaths beyond infancy in developed countries responsible for ~40% deaths in pre-schoolers and ~70% deaths in school-goers or adolescents. Despite underreporting,~30% deaths in school-going children and adolescents in India are estimated to be due to accidental trauma.

Epidemiology: Childhood trauma is relatively uncommon in infancy, with highest risk in 5–9 years age group. Boys are twice more commonly affected than girls. Maximum cases in India may be attributed to *domestic accidents*, e.g. accidental falls from a height, followed by *vehicular accidents*.

Evaluation of pediatric trauma depends on detailed history regarding mode of injury and thorough clinical examination, *soon after* initial ABC of resuscitation.

Following investigations are indicated in all cases of *major* trauma—(a) complete hemogram and blood grouping/cross-matching, (b) urinalysis for hematuria, (c) biochemical evaluation with liver enzymes, renal parameters and electrolytes, (d) arterial blood gases, and (e) radiological evaluation with chest X-ray, relevant skeletal X-rays, USG and relevant CT studies.

Management: Mortality in trauma has a tri-modal distribution with ~50% deaths at the site of event, 30% within a few hours of hospitalizations and 20% after many days due to secondary complications. Consequently, immediate resuscitation is the most important component of trauma care.

General principles of management for a trauma victim are same as discussed previously under CPR (i.e. ABC of resuscitation), followed by revaluation and transfer to appropriate care center.

Pediatric trauma score **(Table 27.20)** is commonly used to decide the severity of trauma and need for PICU care. All cases with PTS < 8 indicate significant trauma and need referral to suitable trauma center. Further management depends on the type and severity of lesion.

One should never forget about medicolegal dimensions of childhood trauma, with due consideration to foul play and child-abuse.

Four major areas of concern in accidental trauma are—(a) head injury, (b) chest-wall injury, (c) abdominal injury, and (d) skeletal injuries and fractures.

TABLE 27.20: Pediatric trauma score

Parameter	*+2*	*+1*	*–1*
Body weight (kg)	> 20	10–20	< 10
Airway	Normal	Maintained	Unmaintained
Systolic BP	> 90	50–90	< 50
CNS	Awake	Obtunded	Coma
Open wound	None	Minor	Major
Skeletal trauma	None	Closed	Open/ multiple

I. Cranio-cerebral trauma: Head injuries may be broadly divided into three categories—(a) superficial soft-tissue injuries of scalp, (b) skull fractures, and (c) brain injuries. Note that *all, even severe, scalp/skull injuries are not necessarily associated with brain injuries. Conversely, serious brain injuries may develop without evidence of external injuries or skull fractures*.

Superficial scalp injuries range from simple abrasions and lacerations to subgaleal/subperiosteal hematoma. As scalp wounds tend to bleed profusely, all major lacerations need suturing as soon as possible.

Skull fractures may be *linear* (single fracture line passing through entire thickness of skull), *diastatic* (>5 mm separation of sutures), *depressed* (an edge displaced posteriorly) and *compound* (with open skin surface).

Clinically, skull fractures may be asymptomatic *or* present with localized bogginess and pain. Important signs of basal skull fractures include—(a) periorbital blackness (*Raccoon eyes*), (b) petechial or subcutaneous hemorrhage on mastoid (*Battle sign*), (c) CSF leak from nose or ears (*CSF rhinorrhea/otorrhea)*, and (d) cloudiness of tympanic membrane (*hemotympanum*).

Diagnosis depends on X-ray skull and CT scan, which is indicated in all head injuries with above mentioned signs of basal skull fractures.

Treatment: *Linear, diastatic or minimally depressed fractures* need no local treatment but indicate severe trauma and possibility of underlying brain injury. However, *depressed fractures of >0.5 cm* require surgical elevation and repair of underlying dura, if necessary. *Compound fractures* or penetrating skull injuries are surgical emergency, which need immediate debridement and prophylactic antibiotic therapy.

Brain injury after head trauma may be due to direct hit or *counter-coup* injury due to sudden movement of brain matter within the closed calvarium.

Younger children are more susceptible for severe brain injury than adults due to—(a) comparatively large head size, (b) open sutures/fontanels, allowing significant shift of brain matter after impact and large hematoma formation before clinical presentation, and (c) relative lack of supporting glial tissue.

Pathogenesis: Important pathogenic factors for brain injury after head trauma include:

- Immediate cerebral vasospasm and reactive neuronal swelling leading to hypoxic-ischemic insult,
- Vasogenic and cytogenic cerebral edema that usually begins after 12–24 hours due to impaired blood-brain barrier,
- Altered cerebral blood flow with intracerebral shunting, and
- Direct vascular injury with bleeding and local hematoma, which may enlarge progressively due to further breakage of bridging vessels.

Types: Common types of neurological injuries after head trauma include:

a. ***Concussion***, i.e. brief period of unconsciousness for few seconds/minutes that occur immediately after trauma, may be associated with retrograde/antegrade amnesia. It is probably result of shearing lesion of white matter due to sudden brain movement and temporary failure of axon conduction.

Though general prognosis after concussion is good, a concussion lasting for >30 minutes *or* followed by focal neurological deficit on recovery indicates significant brain injury. Children with repeated concussion injuries due to abuse *or* contact sports are at risk for permanent brain damage.

b. ***Contusion or laceration*** injuries present with prolonged unconsciousness, raised intracranial pressure and focal neurological deficit. These injuries are usually caused by *counter-coup* mechanism (acceleration-deceleration injury), leading to more severe and diffuse axonal injury and cerebral edema. Early CT scan may be normal and any patient, whose neurological status does not correlate with CT findings, needs MRI that may reveal lesions in corpus callosum, internal capsule or rostral pons. Many cases die in acute phase unless treated intensively, while survivors may improve completely or with residual neurodeficit. Duration of coma after contusion is directly related to mortality and sequelae.

c. ***Epidural hematoma*** is usually associated with linear, diastatic *or* depressed skull fractures due to tearing of middle meningeal artery or bridging veins. These cases typically present with *lucid interval*, i.e. immediate loss of consciousness followed by recovery for few minutes/hours before relapsing again to coma with progressive deterioration. Small epidural hematomas without neurological injury do not need evacuation but follow-up is necessary. Large collections compressing brain tissue or progressive neurological deterioration need surgical intervention.

d. ***Subdural hematoma*** may be acute or chronic. *Acute subdural hematoma* characteristically presents with progressive loss of consciousness and focal

neurological deficits, within few hours of injury. Immediate surgical evacuation is indicated, though prognosis is guarded.

Chronic subdural hematoma is commonest presentation of intracranial hemorrhage in childhood, which may manifest after many weeks or months of injury with—(a) progressive head enlargement, (b) seizures, (c) raised intracranial pressure, and (d) anemia. Treatment includes subdural tapping, and some cases need repeated tapping or subdural shunt.

e. ***Subarachnoid hemorrhage*** is a common cause of post-traumatic hydrocephalus in children. Acute cases may present with signs of meningeal irritation. Treatment is supportive with variable prognosis.

f. ***Intracerebral hemorrhage*** is less likely to be traumatic in origin. Clinical presentation depends on the site and severity of hemorrhage, ranging from complete absence of symptoms *to* focal neurological deficits, seizures and coma, depending on the site of bleeding. Treatment is largely supportive with variable prognosis.

Diagnostic Evaluation of Head Injury

Evaluation of suspected head injury includes local examination for scalp injuries, underlying palpable fractures as well as neurological evaluation. Presence of any one of the clinical features enumerated in **Table 27.21** indicates significant brain injury.

Headache, vomiting, excessive sleepiness or transient dizziness is common after head injuries and not by themselves of concern, if consciousness and neurological examination is normal. However, persistence of these symptoms beyond 24 hours needs further evaluation. *Glasgow coma scale (GCS)* is commonly used to monitor changes in neurological status of these cases **(Table 18.7)**.

CT scan is the investigation of choice in all significant head injuries, which may reveal skull fractures, hematoma, cerebral edema or *mass effect* (mid-line shift). MRI is of little value in acute head injury except to detect very small lesions or diffuse axonal damage and usually reserved for later evaluation and follow-up. Similarly, X-ray skull is hardly informative except for fractures and may be avoided, if CT facility is available.

All cases of head injury should also be evaluated for cervical spine injuries, specially in presence of—(a) significant neck, back or limb pains on movements, (b) acute flaccid para-/quadriplegia, and (c) sensory loss/paresthesia in limbs.

TABLE 27.21: Clinical indicators of brain injury

- Open head injury with exposed brain
- Depressed skull fracture >5 mm
- Progressive deterioration in consciousness
- Unequal pupillary size
- Seizures
- Asymmetric motor deficit
- Persistent otorrhea/rhinorrhea after head injury
- Persistent headache, vomiting, drowsiness >24 hours

General Management of Head Injury

All patients with head injuries should be admitted or at least observed for a few hours before sending home with instructions to report back in case of any change in sensorium, persistent headache/vomiting, seizures or other neurological dysfunction.

Primary aim of the management in head injury after initial resuscitation is to control *cerebral edema* - the major cause of mortality and morbidity. All cases should be managed in head-up position. Continuous intracranial pressure (ICP) monitoring is indicated in all cases with severe head injury with an aim to maintain ICP <20 mm Hg and cerebral perfusion pressure >50 mm Hg, by:

- ***Correction of hypoxia and hypotension,*** which tend to exacerbate abnormalities in cerebral perfusion pressure. Mechanical ventilation is indicated in all cases with GCS <8. However, hyperventilation to maintain pCO_2 at 25–30 mm Hg should be used only in refractory ICP.
- ***Treatment of raised intracranial pressure:*** *IV Mannitol* (0.5–1.0 gm/kg) or 3% Hypertonic saline (IV 5–10 ml/kg) in cases with signs of raised ICP, brain herniation, deteriorating sensorium *or* documented rise in ICP on monitoring, which may be repeated 6 hourly.
- ***Controlled fluid therapy*** with 2/3rd maintenance as Ringer lactate or N/2 saline, due to risk of SIADH. Blood glucose tends to be higher immediately after head injury and dextrose-containing fluids should be restricted during early fluid therapy.
- ***Controlled sedation*** *and muscle relaxation* with barbiturates, e.g. phenobarbitone, midazolam and/or vecuronium is useful to reduce cerebral edema and prevent seizures, as long as hypotension may be avoided. However, prophylactic anticonvulsants are not recommended.
- ***Treatment of fever*** is necessary to minimize metabolic brain requirements. Induced hypothermia has been used to control refractory rise in ICP, though clinical studies are inconclusive.
- ***CSF drainage*** via ventriculostomy is the first-line option for refractory rise in ICP, with/without other neurosurgical interventions, e.g. decompression craniotomy to evacuate mass hematoma. Other options include continuous barbiturate infusion (IV Pentobarbital 5–10 mg/kg over 30 min >1 mg/kg/hr) or controlled hypothermia (32–34°C) by surface cooling.
- Steroids are of controversial value in head injuries and should not be used routinely.

Outcome of head injuries in children is generally worse than in adults and depends on the severity of injury as well as quality of post-traumatic care. Post-traumatic epilepsy, hydrocephalus, meningitis and focal neurological sequelae are common among the survivors.

II. Chest wall injuries: Thoracic injuries may be caused by penetrating or blunt trauma, later being more common and often missed. Many chest wall injuries may also be due to resuscitative efforts.

Four major and life-threatening complications of chest-wall injury include—(a) flail chest due to rib fractures, (b) tension pneumothroax, (c) massive hemothorax, and (d) cardiac tamponade due to hemopericardium.

Clinically, Inadequate response to appropriate cardio-pulmonary resuscitation may be the first sign of chest-wall injuries in children. Important indicators of chest-wall injuries include:

- Acute *or* progressive respiratory distress,
- Restricted/*see-saw* chest movements (*flail chest*)
- Surgical emphysema
- Distended neck veins
- Unresponsive hypotension *or* pulsus paradoxus
- Abnormal respiratory findings
- Muffled heart sounds, etc.

Management: All suspected chest wall injuries need immediate skiagram, and if necessary, diagnostic thoracocentesis to exclude pneumothorax, hemothorax or hemopericardium. Immediate needle aspiration of air/blood from pleural/pericardial space may be necessary in life-threatening emergency, followed by thoracic tube drainage or thoracotomy. Cases with massive hemothorax/hemopericardium should also receive blood transfusions.

III. Abdominal trauma: Blunt abdominal trauma is much more common in children than the penetrating injuries, with most frequently injured organs in descending order being—spleen, liver, genitourinary tract and intestines. Stomach, pancreas, biliary tree, and major vessels are usually injured only in penetrating injuries.

Splenic injury may be indicated by—(a) left shoulder pain that aggravates on pressure over Lt hypochondrium (*Kehr sign*), (b) persistent respiratory distress *or* vomiting, (c) refractory shock due to continued blood loss, (d) peri-umblical blackening (*Cullen sign*). Diagnosis rests on USG/CT with/without radionucleotide scan.

Most cases are managed conservatively with intensive monitoring and transfusions. *Surgical intervention* with splenic repair/splenectomy is indicated in cases with—(a) estimated blood loss of >40 ml/kg during 24–36 hours, (b) complete severance of spleen from its vascular supply, (c) fecal-contaminated hemoperitonium, *or* (d) co-existing head injury, where high volume circulatory support may be dangerous.

Liver injuries contribute to ~40% of deaths due to blunt abdominal trauma and 90% of them involve right lobe of liver.

Spectrum of these injuries, in order of increasing severity and decreasing frequency include – subcapsular hematoma, capsular tears, parenchymal lacerations, and burst injuries with vascular involvement.

Pain over right shoulder *or* hypochondrium is the most important warning signal of probable liver injury, which may be confirmed on USG/CT scan. Management is largely conservative and surgical intervention is recommended only in life-threatening situation.

Renal injuries are frequently associated with other internal organ injuries. Pediatric kidney is more susceptible for trauma due to relatively anterior location, compliant rib cage and immature abdominal musculature. Renal injury with trivial trauma indicates possible congenital malformation.

Important indicators of renal injury include—(a) hematuria with/without oliguria, and (b) renal angle pain/tenderness. Diagnosis rests on urine examination for hematuria, USG and CT with renal contrast.

Treatment is largely conservative and surgical intervention is indicated only in cases with—(a) refractory shock *or* continued fall in hemoglobin, and/or (b) clot-inducted urinary obstruction.

Intestinal injuries are almost always associated with other internal organ injuries and may present with—(a) persistent abdominal pain and vomiting, (b) paralytic ileus, or (c) pneumoperitoneum. Immediate surgical intervention is indicated in these cases.

IV. Musculoskeletal trauma: While some musculoskeletal injuries are common in nearly all cases of trauma, presence of significant fractures or dislocations is indicated by—(a) severe localized pain/tenderness, (b) deformity, and (c) restriction of movements with/without other signs of inflammation.

Children are more susceptible for musculoskeletal injuries due to—(a) relatively more porous bones, (b) developmental laxity of muscles/ligaments, and (c) highly active lifestyle, which renders them prone for injuries, e.g. sport injuries.

Skeletal injuries may be broadly divided into: (a) fractures, and (b) dislocations, e.g. pulled elbow, discussed in Chapter 23.8.

V. Superficial injuries (lacerations, abrasions and cuts): Lacerations are superficial skin tears due to blunt or shearing force, while cuts and stabs are caused by sharp objects. Abrasions are mere scrape of the skin due to friction against a hard surface. These injuries may be accidental or intentional and medico-legal consideration must be taken into account while managing them.

Management of these injuries involve—(a) local wound examination and management, (b) general supportive

measures including pain relief, and (c) exclusion of underlying deeper injuries.

All cuts and lacerations must be thoroughly examined for the size and depth of the wound, presence of any foreign body and associated vascular, neurologic, tendon, or other tissue injury. Initial goals of treatment are to establish hemostasis, minimize infection and restore skin integrity. Any significant bleeding must be controlled with external pressure or tourniquet. Skin flap, if any, must be returned to original position before application of pressure.

Subsequently, contaminated wounds must be irrigated with water or normal saline and dead tissues must be removed. Local wound care may need a topical anesthetic or regional nerve block before manipulation. Most superficial lacerations and cuts may be closed primarily with non-absorbable sutures, staples, skin adhesives or surgical tapes; followed by topical antimicrobial ointment and gauze dressing to prevent infection.

Prophylactic antibiotics are unnecessary and indicated only in open or grossly contaminated wounds or human/animal bites. Tetanus prophylaxis is indicated in unimmunized or partly immunized cases.

27.5.2 BURNS AND SCALDS

Burns are common household accidents in children, including *flame-burns*, *wet-burns* (scalds) due to hot liquids and *fume-burns*, e.g. carbon monoxide (CO) poisoning. Most cases are accidental, though intentional burns (child abuse, *Branding*) are not uncommon.

Classification: Burns are classified according to the depth and extent of lesions, to assess their severity, need for hospitalization, fluid requirements and prognosis.

Depth-wise, burns are classified as:

- *First-degree* burns, limited to epidermis only. These burns present with local pain, erythema and swelling, *without blisters* and usually heal within 7 days without scarring.
- *Second-degree* burns involve entire epidermis and part of dermis. These burns are extremely painful due to exposure of viable nerve endings and heal in 1–2 weeks with scarring, unless infected.
- *Third degree* (full thickness) burns denote destruction of entire epidermis and dermis. Pain is minimum in these cases due to destruction of nerve endings. The wounds cannot epithelialize spontaneously and heal only by contraction scar *or* after skin grafting.

Extent-wise, burns are denoted in terms of percentage of body surface area **(Table 27.22)**. Conventional *rule of 9* in adults, is not applicable in children below 12 years.

Management: of burns include on-site management and hospital therapy.

TABLE 27.22: Calculation of % burn in children

Burnt part	*0–3 years*	*3–6 years*	*6–12 years*
Head	18%	15%	12%
Trunk	40%	40%	40%
Arms	16%	16%	16%
Legs	26%	29%	32%

On-site first-aid includes—(a) extinguish the fire by rolling-over the patient *or* covering with a blanket, (b) ensure airway patency, (c) remove non-adherent clothing, (d) irrigate affected parts with cold, clean water, (e) cover the affected parts with a dry-clean sheet, and (f) transfer to the nearest hospital.

Hospitalization is indicated in all cases with: (a) burns >10–15%, (b) burns involving face, neck, perineum, joints and hand/feet, (c) electrical/lightening burns, (d) suspected smoke inhalation, and (e) child abuse. Remaining cases can be managed on outdoor basis with local cleaning/dressing and mild analgesics, e.g. paracetamol or codeine. *Intact blisters should not be punctured.*

Management of severe cases include:

- ***Cardiopulmonary resuscitation,*** ensuring airway patency, ventilatory and circulatory support.
- ***IV Fluid therapy*** in all cases with >15% burns, to replenish fluid losses due to interstitial edema, tissue injury and plasma loss. As the amount of fluid loss depends on the severity of burn, first-day fluid requirement is calculated as 4 ml/kg/percentage of burn- half of which is to be given in first 8 hours and rest in next 16 hours (*Parkland formula*).

  By second day, reabsorption of interstitial edema starts and only half of the first-day fluid amount is necessary, unless indicated otherwise on clinical or biochemical monitoring. Colloids, e.g. blood plasma, albumin, etc. may be used for volume replacement on 2nd day in cases with >85% burns.
- ***Electrolyte correction*** is required for *hyponatremia* (due to extracellular fluid loss) and *hyperkalemia* (due to extracellular movement of K^+ from injured tissues) - two most common electrolyte disturbances in burns.
- ***Prevention of infection*** is essential with—(a) barrier nursing, (b) topical dressings, (c) excision of dead tissue, (d) prophylactic antibiotics, and (e) early tissue grafting. *Nosocomial infections*, specially due to *Psuedomonas*, are leading cause of late morbidity and mortality in burns.
- ***Enteral feeding*** may be started orally *or* via nasogastric tube after 48 hours in most cases. Due to higher requirement for tissue regeneration, ~150% of normal caloric requirement and 3–4 gm/kg of proteins per day is recommended.

- ***Inhalation injury*** due to hot/toxic fumes, asphyxia and CO poisoning, presents with pulmonary edema within few hours and ARDS after 24–48 hours. Symptoms of CO poisoning correlate well with HbCO levels, ranging from mild dyspnea and cloudy sensorium (HbCO<20%), to confusion and diminished vision (20-40%) and coma (> 40%).
- ***Pain-relief*** is usually provided with benzodiazepines, though morphine may be needed in severe cases.
- ***Topical therapy*** includes local application of bacitracin or silver sulfadiazine cream or ointment without dressing in mild cases. Blisters should not be punctured. Second-degree or deeper burns often need debridement of overlying dead skin, followed by silver-impregnated wound dressings.
- ***Reconstructive surgery*** and rehabilitation is essential part of late management in severe burns to improve the quality of life.

Outcome of burns depend on their severity, co-existing inhalation injury, appropriate early therapy and nosocomial infections.

27.5.3 DROWNING AND NEAR DROWNING

Drowning is defined as 'death within 24 hours of submersion in a water body', while survival or death after 24 hours is termed as *near-drowning*. Drowning/near drowning in children is almost always accidental and may occur at home (bucket-drowning), swimming-pools *or* open water bodies, e.g. rivers, lakes and sea.

Risk factors for drowning accidents are: (a) *age* – toddlers or male adolescents, (b) *medical conditions*, e.g. epilepsy, motor disability or mental retardation, (c) *drug abuse* or sedation due to therapeutic drugs, and (d) *child abuse* or neglect.

Pathophysiology of drowning is characterised by three major pathological events: (a) sudden hypoxic-ischemic brain injury, (b) pulmonary aspiration, and (c) hypothermia; followed by *secondary* disturbances, e.g. fluid/electrolyte imbalance, progressive respiratory failure, neurological abnormalities and secondary infections.

Hypoxic-ischemic brain injury is caused by—(a) sudden choking due to protective laryngospasm, (b) failure of *diving reflex* to sustain blood supply to the brain, and (c) myocardial ischemia due to progressive respiratory failure. Raised intracranial pressure, seizures and altered sensorium from confusion to coma, are common features of hypoxic-ischemic brain injury.

Pulmonary aspiration occurs in ~80-90% incidents and pathological consequences depend on the amount, salinity and contaminants in aspirated water. Sea-water drowning leads to acute pulmonary edema due to its hypertonicity. Drowning also washes away the lung-surfactant, leading to alveolar collapse, ventilation-perfusion mismatch and ARDS.

Hypothermia develops due to contact with cold water (conductive heat loss) before rescue and convective/radiative heat loss from wet body after rescue. While hypothermia is protective to some extent due to reduced metabolic demands, in most cases it accentuates hypoxia due to shivering and increased sympathetic tone. Severe hypothermia (<32°) is nearly fatal.

Management of drowning/near-drowning depends on the clinical state of the child immediately after rescue, who may be asymptomatic, frightened/agitated, or unconscious. Important components of management include:

On-spot first aid with:

- Immediate clearance of airways for foreign bodies.
- Positioning in prone, head-low position with head turned on one side, to prevent aspiration.
- Basic cardiopulmonary resuscitation, including breathing assistance (mouth-to-mouth breathing).
- Gastric deflation with nasogastric tube, if available.
- Prevention of hypothermia, using blankets/sheets.
- Immediate transport to the nearest hospital.

Abdominal thirsts *or* thoracic compressions to remove swallowed water should be avoided in a spontaneously breathing child, unless airway obstruction *or* foreign body is suspected due to risk of further aspiration.

Hospital care in these cases is guided by clinical assessment of vital signs on admission and subsequent monitoring. Fully alert and breathing children may be sent home after initial assessment, as late sequelae are unlikely. Other cases require:

- *Quick clinical assessment* for vital signs and neurological status
- *Cardiopulmonary resuscitation* with—(a) *airway* suction and endotracheal intubation, if needed, (ii) *breathing* support with oxygen/ventilatory assistance, and (c) *circulatory* support with IV fluids and vasopressors.
- *Re-warming* in a hypothermic child needs to be done cautiously, as only *surface-warming* with blankets or warmers may precipitate shock due to movement of blood into dilated surface vessels. C*ore-warming* may be achieved with warm IV infusions and warm gastric lavage.
- *Fluid and electrolyte correction* is guided by clinical and biochemical findings. Massive sea-water aspiration leads to hypernatremia and hemoconcentration (osmotic effect); while fresh-water aspiration leads to hyponatremia, hemodilution (water intoxication), and hyperkalemia (cell lysis).
- *Neurological complications* may require anti-edema measures, e.g. mannitol or furosemide, anticonvulsants and supportive therapy.

- *Prevention of secondary infections* with appropriate use of antibiotics.
- Treatment of other injuries, e.g. fractures.
- Psychiatric *or* psychosocial support

Outcome depends on: (a) duration of submersion, (b) effectiveness of on-spot resuscitation, and (c) clinical state on admission. Development of raised ICP and ARDS are worst prognostic indicators. Although ~80% cases survive drowning accidents, neurological residue may develop in ~10%.

27.5.4 FOREIGN BODY ACCIDENTS

Accidental ingestion, inhalation or aspiration of foreign bodies is the commonest accident in toddlers (1–3 years) due to their inquisitive and exploratory behavior, more common in boys (2:1).

While the list of foreign bodies is endless, ~3/4th of them are *organic* (peanuts, whole grains) which are not detected on X-rays, unlike *inorganic* foreign bodies, e.g. coins and buttons.

Clinical presentation and complications of foreign body accidents depend on: (a) type of the body, (b) size and shape, (c) site of lodgement, and (d) duration.

Nasal foreign bodies are most common in toddlers, usually being grains or peanuts. These bodies may present immediately after lodgment with definite history or after many days with unilateral foul-smelling discharge, swelling and noisy breathing. Local *trauma, aspiration* and rarely *tetanus* are potential complications in these cases.

Most of these bodies are easily visible with a nasal speculum and may be removed by—(a) forcible blowing of the nose, (b) wet cotton bud, or (c) forceps after local xylocaine and decongestant instillation. Long-standing, sharp, embedded *or* posteriorly located bodies need removal by an ENT surgeon under rhinoscopic guidance, as blind attempts may push them further down with risk of aspiration.

Ear foreign bodies are common in all groups, usually being insects or left-over cotton buds. These bodies usually present after many days with earache, discharge, tragus swelling, ringing sensation or temporary deafness. *Ear-drum injury/perforation* and *tetanus* are important risks of aural foreign bodies.

Due to late presentations, these bodies may be impacted and tend to move deeper on attempted blind removal. Unless visible externally, long-standing bodies should be referred to ENT surgeon for otoscopic or surgical removal.

Pharyngeal foreign bodies are usually fish-bones, presenting with dysphagia *or* prickly sensation in throat. Most of them are easily visible and removable by *Tongue-jaw lift maneuver* (Ch 27.1). However, blind finger-sweeps should not be performed due to risk of pushing them further into airways.

Laryngeal foreign bodies are common cause of sudden accidental deaths in preschool children, even if very small in size due to reactive laryngospasm and edema. These cases present with sudden choking, dyspnea, stridor or croup. *Whistle sign*, i.e. a whistling sound on inspiration and expiration is diagnostic in laryngeal obstruction due to toy whistles—a common foreign body. Considering immediate risk of death, basic first-aid measures, e.g. *Back-blows and chest thrust maneuver* in infants and *Heimlich maneuver* in older children may be attempted, provided: (a) foreign body is witnessed or strongly suspected, (b) expert help is not immediately available (Ch 27.1). Spontaneous coughing should be encouraged. As these procedures carry risk of converting partial airway obstruction to complete block and sudden death, expert help must be sought as early as possible.

Diagnosis of laryngeal foreign body may be confirmed on direct laryngoscopy *or* lateral X-ray of the neck (d/d esophageal foreign body), which then can be removed by endoscopy. Tracheostomy is advisable before laryngoscopy in severe dyspneic children.

Bronchial foreign bodies may be entirely asymptomatic in early stages or present with signs of airway irritation or obstruction, e.g. cough, dyspnea, blood-streaked sputum or recurrent respiratory infections. History of foreign body inhalation is often absent. Bronchial foreign bodies are more common on right side due to straight bronchus.

Clinico-radiological signs depend on the extent of airway obstruction, with two distinct pathologies—(a) incomplete obstruction with ball-valve mechanism, leading to obstructive *emphysema*, and (b) complete obstruction with distal *collapse*.

Bronchoscopic removal with a rigid bronchoscope, followed by check X-rays is the treatment of choice in these cases. Rigid bronchoscope is preferred due to wider lumen and separate oxygen channel. Overall risk of mortality with bronchoscopy is <2% in expert hands though complications, e.g. failure to locate foreign body, local trauma/bleeding and sudden hypoxia/apnea are common.

While most collapse/emphysema improve rapidly after foreign body removal, persistent lesions may require lobectomy due to risk of recurrent infections.

Esophageal foreign bodies present with dysphagia or retrosternal pain due to esophagitis and tend to rest at one of the *three* sites of physiological narrowing – below the cricopharynx, at the level of aortic arch and just above the diaphragm. Preliminary diagnosis depend on history and X-ray neck/chest to visualize radio-opaque bodies.

Management of esophageal foreign body depends on its size and shape as well as clinical symptoms. Non-sharp small foreign bodies, e.g. coins, tend to pass

spontaneously, facilitated by ingestion of lubricants, e.g. banana or ghee. Esophagoscopic removal is indicated for sharp, toxic or symptomatic foreign bodies.

27.5.5 SNAKE BITE

Snake bite is a common accident in rural India, though majority of them are by non-poisonous snakes. Poisonous snakebites (envenomation) are often fatal, unless treated promptly and adequately .

Incidence of snakebite depends on human–snake interaction, being more common in older children, males and rural, tribal or coastal regions. Although underreported, snake envenomation is responsible for ~5000 deaths annually in India, commonest being in Maharashtra, West Bengal and Tamil Nadu.

Types: According to herpetologists, ~300+ species of snakes exist in India, of which only 20% are poisonous, usually belonging to four species: (a) *elapidae*, e.g. cobra, kraits, coral snakes, etc., (b) *viperidae*, e.g. saw-scaled viper, Russel-viper, etc., (c) *crotalidae*, e.g. pit vipers and (d) *Hydrophidae*, e.g. sea-snakes. Vipers, cobra and kraits are commonest offending snakes in India, responsible for ~50%, 25% and 15% poisonous bites, with following important features:

Viper has a flat, triangular head with long and mobile front fangs, vertical pupils and usually diamond-shaped black/brown spots over body. These snakes injects ~15–60 mg of venom/bite (lethal dose 8–15 mg), which is mainly hematotoxic, leading to hemolysis, bleeding and DIC.

Cobra is characterized by oblong head with fixed front fangs, cephalic hood with 'spectacle' mark and long-tapering tail. They generally inject ~60 mg of venom/bite (lethal dose 12 mg), which is predominantly neurotoxic or cardiotoxic.

Kraits are smaller but most poisonous snakes with flat head, fixed front fangs and steel-blue body with white cross bars or yellow body with black cross bands. They injects ~15 mg of venom/bite (lethal dose 6 mg), which is predominantly neurotoxic or cardiotoxic.

Sea-snake bites are common in coastal regions, characterized by severe rhabdomyolysis, myoglobinuria and renal failure.

Pathophysiology: Although species-specific, Snake venom is a mixture of many *enzymes*, which damage tissue barriers and *toxins*, e.g. neurotoxins, hemotoxins, cardiotoxins and myotoxins.

Venom from elapidae and hydraphidae snakes is primarily neurotoxic, with a *curare-like* effect, i.e. blockade of transmission across the neuromuscular junctions, leading to paralysis and respiratory failure.

Viper-venom is predominantly cytotoxic or hemotoxic, leading to massive tissue necrosis, vascular leaks and coagulopathies followed by shock, ARDS and renal failure.

TABLE 27.23: Determinants of severity in snake bite

- Age (more severe in children)
- Species of offending snake
- Site of bite (more severe face and trunk bites)
- Amount of venom injected:
  - Number and depth of fang marks
  - Bites over uncovered areas (e.g. bare-foot)
- Spread of venom
  - ↑ due to running* after the bite
  - ↓ due to immediate torniquet application
- Quality of first-aid

*increases local vascularity

Clinical manifestations of a poisonous snake bite usually begin within 15–30 minutes, though may be delayed as much as 24–48 hours, depending on various factors **(Table 27.23)** and include:

- ***Asymptomatic bites*** by non-poisonous snakes, 'dry bites' or bites over covered areas, e.g. shoes.
- ***Local manifestations,*** e.g. burning pain, swelling, bullae formation or gangrene.
- ***Systemic manifestations*** depending on the species of snake and include:
  - *Neurological:* Drowsiness, ptosis, dysarthria, dysphagia, bulbar palsy and progressive flaccid paralysis, terminating into coma.
  - *Hemorrhagic:* Purpura, hematuria, hemoptysis, hematemesis, intracranial bleeding or DIC.
  - *Cardiovascular:* Hypotension, shock or arrhythmia.
  - *Muscular:* Myalgia, myoglobinuria > renal failure.

Untreated cases with systemic manifestations often die within 24-48 hours, while dramatic recovery is common after anti-snake venom (ASV) therapy. However, many ASV responders develop recurrence of symptoms after 24-48 hours due to ongoing venom absorption from the local site or clearance of ASV (half-life 1–4 hours).

Diagnosis mainly aims to differentiate between poisonous and non-poisonous bites, depending on the - (a) examination of killed snake, if possible, (b) fang marks, and (c) clinical presentation. *Presence of 2–4 clear and deep fang marks (1–8 mm depth), without other teeth impressions indicates poisonous bites*.

In addition, relevant laboratory investigations are necessary to monitor and prognosticate the course of illness, including—(a) *blood profile* for hemolysis, thrombocytopenia and clotting defects, (b) *metabolic profile* for hypokalemia, hypoxemia and acidosis, (c) *urine examination* for hematuria, hemoglobinuria or myoglobinuria, and (d) *ECG* for arrhythmia.

Management: All snake bites should be considered as potentially poisonous and need basic first-aid as well as earliest hospitalization for observation till minimum 24 hours. Important steps in management include:

a. ***Immediate first-aid*** with—(a) *reassurance and immobilization* as any muscular activity tends to

increase the spread of venom, (b) application of a *wide tourniquet*, proximal to the bite to block lymphatic and venous spread, (c) *local incision* of 1.0 × 0.5 cm size within 15 min of bite, (d) *irrigation* of local wound with saline and (e) *referral* to nearest hospital.

b. ***General supportive measures*** on hospitalization include: (a) ABC of *resuscitation*, (b) *fluid and electrolyte therapy* (preferably with colloids, e.g. plasma/blood, as crystalloid solutions may be lost to extravascular space due to increased capillary permeability), (c) *tetanus toxoid*, (d) prophylactic *antibiotics*, and (e) *supportive therapy*. Steroids are not indicated and sedation should be avoided during early stages.

IV Neostigmine is useful in selected cases of neurotoxin-induced paralysis, while *heparin therapy* may be needed in those with DIC-like manifestations. Recent studies have reported beneficial effects of IVIG therapy in cases with coagulopathy, but not in those with neurotoxic manifestations.

c. ***Anti-snake venom*** (ASV) is indicated only in—(a) bite by a identified poisonous snake, (b) serious systemic manifestations or laboratory abnormalities, (c) extensive and rapidly progressive local reaction. Risk of common (~5%) and occasionally fatal hypersensitivity reactions precludes ASV therapy in all cases of snake-bite.

Presently, a polyvalent ASV of equine origin is available in India as freeze-dried powder, which needs to be dissolved in 10 ml of saline/vial, before use. While exact dose is not established, 50–150 ml of reconstituted ASV (5–15 vials) must be infused slowly @ < 2 ml/min. Sensitivity testing is not necessary and delays the therapy. However, resuscitation measures to manage anaphylaxis must be ready. Clinical response in neurotoxic cases is often dramatic with near-normal recovery within 15–30 minutes, though repeat doses are necessary in many cases. Normalization of clotting time is taken as end-point of ASV therapy in hemotoxic cases, though clinical recovery may take many days.

Prognosis: Overall mortality with snake envenomation is ~10–20%, depending on the severity of manifestations and quality of first aid/hospital care. In recovered cases, local and mild systemic abnormalities may persist for many weeks.

27.5.6 SCORPION STING

Scorpion sting is more common than snake-bite in rural and costal regions of India, though mortality is rare except in young children. Out of ~80 species in India, only two scorpions are toxic - *Mesobuthus tamulus* (red scorpion) and *Palamnaeus swammerdami* (black scorpion).

Pathophysiology of scorpion-sting is related to:

- Release of chemical mediators, e.g. catecholamines (*automonic storm*), cytokines and platelet-activating factors; and,

TABLE 27.24: Complications of scorpion sting

- ***Local reactions***
- ***Transient autonomic storm*** (< 6 hours)
- ***Late systemic reactions*** (> 6 hours)
  - *CVS:* Myocarditis, arrhythmia, heart blocks
  - *Resp.:* Pulmonary edema, ARDS
  - *CNS:* Acute encephalopathy, seizures, stroke
  - *Blood:* DIC, bleeding tendencies
  - *Renal:* Hematuria, renal failure
  - *Others:* Anaphylactic shock, hypoglycemia

- Altered permeability of cell membranes, specially at pre-synaptic terminals, due to stimulation of sodium channels and inhibition of calcium-dependent potassium channels.

Sympathetic α-*receptor stimulation* appears to be the critical event in systemic manifestations of scorpion sting, which may be blocked by competitive antagonists, e.g. *Prazocin*.

Clinically, most scorpion stings are limited to local reactions, e.g. burning pain, itching, swelling or ecchymosis, lasting for 24–48 hours. Systemic reactions are more common in young children or some adults, which begin as "***autonomic storm***" within a few minutes to 6 hours of envenomation, characterized by tachycardia, hypertension, perspiration, mydriasis and hyperglycemia. *Priapism*, due to sympathetic vasodilatation of penile vascular bed is a useful indicator of autonomic storm in scorpion sting.

Untreated cases may deteriorate rapidly with complications due to: (a) myocardial dysfunction, e.g. hypotension, shock and arrhythmia, and (b) increased capillary permeability, e.g. pulmonary edema and ARDS **(Table 27.24)**. Overall mortality is <2%.

Diagnosis depends on history, examination of scorpion if possible and clinical evaluation for signs of autonomic storm or systemic complications with relevant investigations.

Management: Hospitalization is preferable in all but mildest scorpion bites till 24 hours for close supervision. Currently, no anti-scorpion venom is available in India and treatment is largely supportive and symptomatic, with following steps:

a. ***Local pain relief*** to allay anxiety and myocardial stress with Diazepam (PO/IV 0.5–2.0 mg/kg). Local infiltration of xylocaine is useful in severe cases.

b. ***Treatment of autonomic storm*** with Prazocin (PO 30 µg/kg/dose at 0, 3, 6 hours). *Prazocin*- α-1 adrenergic antagonist, decreases myocardial load by peripheral vasodilatation as well as counteracts metabolic effects of adrenergic stimulation. It should be started as soon as first sign of autonomic storm appears, though prophylactic therapy is not advisable. *Calcium-channel blockers*, e.g. verapamil and/or *ACE*

inhibitors, e.g. nifedipine may also be used in cases with severe hypertension.

c. ***Myocardial dysfunction*** usually manifests after 6–24 hours with hypotension and poor perfusion (cold extremities), which needs oxygen supplementation, fluid/electrolyte correction, inotropic agents, e.g. dopamine and after-load reducing agents, e.g. IV sodium nitroprusside (2–5 mg/kg/min).

d. ***Pulmonary edema and ARDS*** are other important complications, which needs positive pressure ventilation, along with other supportive measures.

27.5.7 HEAT INJURIES

Heat injuries is a collective term to denote "many illnesses associated with acute *or* prolonged exposure to excessive heat", due to—(a) high environmental temperature in tropical countries during summer season, (b) endogenous heat over-production during strenuous exercise/sport activities, (c) defective dissipation of body heat by radiation (excessive clothing) or evaporation (impaired sweating), or (d) impairment of thermoregulatory mechanisms.

Only 25% of energy produced during by muscular contraction is utilized for actual work, while rest is converted into heat. Body dissipates this heat by radiation (60%), evaporation (25%) and convection.

Children are more susceptible for heat injuries due to—(a) immature heat-elimination mechanisms, e.g. poor sweating, and (b) excessive endogenous heat generation due to sports/outdoor activities. However, children have adequate capability to acclimatize after prolonged heat exposure.

Clinical manifestations of heat injuries depend on the severity, duration and individual cooling mechanisms. Important heat injuries include:

- ***Heat cramps*** in calf and hamstring muscles, are most common manifestations of minor heat injuries, usually seen after strenuous exercise due to electrolyte imbalance following sweating and ingestion of hypotonic fluids, e.g. water. These cramps respond well to oral rehydration with electrolyte solutions (1 tsf salt/500 ml water) and gentle stretching of muscles.
- ***Heat syncope,*** i.e. fainting after prolonged standing/exercise in hot and humid environment, e.g. school assemblies, is attributed to depleted intravascular volume and peripheral pooling of blood after cutaneous vasodilatation. Placing the child in supine position under cool-shade is usually enough to recover from these attacks, which may be prevented by consuming plenty of fluids.
- ***Heat edema*** over hands/feet during initial exposure in hot environment is more common in adults than in children and usually subsides spontaneously after some time.
- ***Heat tetany***, i.e. carpopedal tingling or spasm, is related to heat-related hyperventilation with subsequent alkalosis, which responds to shifting the child in cooler environment and re-breathing into a paper-bag.
- ***Heat exhaustion*** is usually seen after prolonged exposure to moderately hot and humid weather, due to progressive fluid and salt depletion.
- ***Heat-stroke,*** a potentially life-threatening heat injury, which may be fatal in ~50% cases unless recognized and treated promptly, discussed later.

Clinically, these cases present with headache, fatigue, nausea/vomiting, vertigo, dehydration and postural hypotension. Fever, though common, is *not a must* for diagnosis of heat exhaustion and CNS signs are characteristically absent (*d/d heat stroke*).

Treatment includes shifting the case to cooler environment, cold-sponging and administration of adequate fluids and electrolytes via PO/IV route.

Heat stroke (hyperpyrexia) is of two types—(a) *classic heat stroke*, which is mainly seen in elderly and chronic debilitated patients, exposed to summer heat wave, and (b) *exertional heat stroke*, which is usually seen in children/adolescents after unacclimatized exercise.

In India, heat stroke is common in hot and humid months of April to July, with preceding history of prolonged outdoor activity/sport participation.

Pathophysiology of heat stroke relates to unexplained failure of thermoregulatory mechanisms and elevation of hypothalamic thermostat, which prevents activation of heat-dissipation mechanisms, e.g. sweating. Although the exact mechanism for this failure is unknown, an energy-depletion model has been suggested (excessive heat production > over-activation of Na^+/K^+ ATPase pump > excessive sodium efflux from the cells > depletion of cellular energy, essential for thermoregulation).

Clinically, heat stroke may be sudden or preceded by a brief prodrome of headache, nausea/vomiting and dizziness, characterized by a triad of:

- *Hyperpyrexia* with core-temperature > 40°C,
- *Neurological dysfunction* with delirium, coma, tremors, seizures, muscular rigidity, etc.,
- *Dry, flushed skin* with absence of sweating. However, sweating may be present in exertional stroke in young children.

Other important and late manifestations include: (a) *cardiovascular* manifestations, e.g. tachycardia, shock or CCF due to myocardial injury, (b) *hepatic* manifestations, e.g. jaundice or elevated transaminase levels, (c) *coagulopathies*, e.g. purpura, conjunctival hemorrhage, orificial bleeds, (d) acute renal failure, (e) *lactic acidosis* with respiratory alkalosis, and (f) *metabolic/electrolyte disturbances*, e.g. hypoglycemia, hypokalemia, hypernatremia and hypocalcemia.

Diagnosis depends on: (a) history of heat exposure, (b) clinical triad, as above, (c) exclusion of other causes for hyperpyrexia with CNS signs, e.g. cerebral malaria, CNS infections and *dhatura* or *atropine* poisoning.

Management: Heat stroke is a medical emergency that needs immediate hospitalization and intensive care. Primary aim of the management in these cases is the *rapid body cooling*, followed by hemodynamic and metabolic stabilization and treatment of complications. Important steps include:

- ***External body cooling*** by: (a) shifting the patient in cooler environment with removal of cloths, (b) whole body immersion in ice-cool water except the head, (c) evaporative cooling by placing large fans near the patient's body. Many PICUs in hot-humid regions, where heat stroke is common in summers, have specially designed body-cooling units for this purpose.

  Other cooling methods, e.g. gastric/rectal lavage with cool water, application of ice-packs, etc. may be used. Vigorous shivering during rapid cooling may be controlled by chlorpromazine, if necessary.

  Antipyretics are contraindicated in heat stroke, which may worsen hepatic and hematological injury.
- ***Hemodynamic support:*** Hypotension is common due to peripheral vasodilatation, which usually improves with peripheral cooling. However, persistent hypotension/shock need appropriate fluid replacement and inotropic support under hemodynamic supervision, e.g. CVP monitoring.

  α-adrenergic drugs, e.g. noradrenaline, should not be used, which may cause cutaneous vasoconstriction and reduce heat loss.
- ***Treatment of complications***, e.g. seizures (diazepam), coagulopathy (transfusions), acute renal failure and metabolic disturbances, depending on the laboratory values.
- ***Post-recovery monitoring:*** All patients should be closely monitored for 24–48 hours for temperature, vital signs, urinary output, biochemical parameters, e.g. attacks, which may be prevented by consuming plenty of glucose, liver transaminases, urea/creatinine, serum electrolytes, and ABG, to detect late complications, e.g. coagulopathy or liver damage.

27.6 POISONING IN CHILDREN

Poisoning is a common medical emergency and important cause of death in children. Unlike adults, most cases of childhood poisoning are accidental in origin and usually seen in toddlers due to their inquisitive and exploratory nature. Intentional poisoning, e.g. suicidal attempts, are not uncommon in adolescents, while intentional homicidal poisoning is rare but does occur.

Accidental exposure to unwanted substances is common in young children, though most of these substances are non-poisonous. While the pattern of accidental poisonous exposures depends on family environment, some common poisons in Indian children, in order of the frequency of exposure, are: (a) hydrocarbons, e.g. kerosene, (b) drugs and medications, (c) insecticides/pesticides, (d) detergents, and (e) others. The pattern of poisoning also differs in urban vs. rural population.

TABLE 27.25: Epidemiological risk factors for poisoning

- Younger age (< 3 years)
- Male sex
- Large family size
- Illiterate or working parents
- Overcrowded dwellings e.g. slums
- Mentally handicapped or hyperactive child
- *Seasonal:* CO (winter), pesticides (harvesting)
- Domestic/household industries
- Child labor in hazardous industries
- *Family events:* House-painting, change of residence

CO: Carbon monoxide poisoning

Accidental childhood poisoning is more common in males and ~75% cases occur in first 3 years of life, with maximum risk (40%) during second year. Common epidemiological risk factors for poisoning are given in **Table 27.25**.

27.6.1 GENERAL PRINCIPLES OF MANAGEMENT

Poisoning must be suspected in any cases with: (a) hyper-acute onset of symptoms in a previously healthy child, (b) clinical presentation unexplained by common disorders, and (c) multisystemic involvement without obvious reason.

All cases exposed to unknown or presumably poisonous substances, even if asymptomatic, need to be hospitalized and observed for at least 24 hours of exposure to detect later presentations.

While specific management of each case differs according to the type of poison-exposure, some general principles are as follows:

Step I. Immediate resuscitation is the first priority in cases of severe poisoning, irrespective of the cause and involves general principles (ABC) of resuscitation, i.e. measures to restore airway, breathing and circulation.

Step II. Quick clinical evaluation involves:

a. *History* regarding—(a) probable nature of the poison, (b) approximate quantity/dose ingested, (c) timing of the exposure, (d) progression of symptoms.
b. *Clinical examination* for vital signs and probable indicators for specific poisoning. Considering the commonality of clinical features in many poisonings, a *toxidromic approach* is useful to categorize the clinical picture and limit diagnostic possibilities in unknown poisons **(Table 27.26)**.

TABLE 27.26: Common toxidromes (symptom complexes) in poisoning

Toxidrome	*Pupil*	*HR*	*BP*	*Resp*	*CNS*	*Others*
1. Cholinergics (OP compounds, tobacco)	C	↓	↓	Bronchospasm	Mus. weakness/ twitching, coma	Lacrimation, salivation, urination, vomiting/ diarrhea
2. Anticholinergics (Atropine derivatives, anti-histamines/depressants)	D	↑/Ar	↓↓	↑	Excitation, seizures	Fever, thirst, dry/ flushed skin, urinary retention
3. Sympathomimetics (Amphetamine, cocaine, PPA, theophylline)	D	↑	↑	↑	Excitation, seizures hallucinations	Hyperpyrexia, acidosis
4. Narcotics (Opioids, benzodiazepines, barbiturates)	C	↓	↓	↓↓	Sedation	Hypothermia
5. Narcotic withdrawal	D	↑	↑/↓	↑/yawn	Restlessness, Hallucinations	Abd. cramps, diarrhea, lacrimation, sweating
6. Extrapyramidal (Phenothiazines, haloperidol, antiemetics)	–	–	–	–	Tremors, Dystonia	–
7. Hypermetabolic (Salicylates, phenols)	N	↑	↑	↑↑		Hyperpyrexia, R. alkalosis > M. acidosis

C: Constricted; **D:** Dilated; **Ar:** Arrhythmia; **OP:** Organophosphorus; **PPA:** Phenylpropalamine; **B'spasm:** Bronchospasm

Step III. Prevention of absorption: Further absorption of an ingested or contacted poison may be reduced by following measures:

a. **Gastrointestinal decontamination** intends to reduce the absorption of ingested substances, though its role in cases with low-dose exposures or late presentations is controversial. Common methods of gastric decontamination include:
   - ***Forced emesis***, is ***not recommended*** for routine use in poisoning. It is specially contraindicated in—(a) infants < 6 months *or* comatose children due to poor gag reflex, (b) corrosive poisoning, (c) kerosene poisoning, or (d) sharp foreign body ingestion.
   - ***Gastric lavage*** with 10–15 ml/kg of normal saline is indicated in—(a) large volume ingestion of poisonous substances, (b) patient presenting within 60 minutes of ingestion, (c) obtunded patients, who require endotracheal intubation. Gastric lavage also helps in identification of ingested poison, especially in medicolegal cases. However, it is of controversial value in asymptomatic cases *or* those who present after one hour of ingestion, except pesticide poisoning (up to 6 hr) or ingestion of sustained release preparations (upto 12 hours).

     Gastric lavage is *contraindicated* in—(a) corrosive poisoning, (b) hydrocarbon poisoning, and (c) very young/comatose children with poor gag reflex, due to potential risk of aspiration, esophageal injury and laryngospasm.
   - ***Activated charcoal*** - a wood distillate with large absorptive surface area, is the main stay of gut decontamination and prevention of further toxin absorption. For maximum benefit, 1–2 gm/kg of activated charcoal slurry should be given along with a cathartic, e.g. sorbitol or magnesium compound, within one hour of ingestion. Multiple doses may be used in select cases with added benefit of enhanced enterohepatic circulation. If slurry is not available, crushed charcoal tablets mixed with saline may be used.)

     Activated charcoal is not effective in poisons, which are not adsorbed by it, e.g. heavy metals, corrosives, hydrocarbons, iron, lithium, alcohol, and water-insoluble compounds. It is *contraindicated* in cases with suspected paralytic ileus or mechanical intestinal obstruction.

     Universal antidote, containing *activated charcoal* as general adsorbent (2 parts), *magnesium hydroxide* to neutralize acids (1 part) and *tannic acid* to neutralize metals or weak alkalis/alkaloids (1 part), is ***no longer recommended*** to prevent absorption of poisons.
   - ***Cathartics***, e.g. Sorbitol (1–2 gm/kg) or Polyethylene Glycol (8.5 gm sachet in water) alone have no role in gut decontamination and should be used only with activated charcoal therapy.
   - ***Whole bowel irrigation*** with 20–40 ml/kg/hour of non-absorbable electrolyte solution, e.g. *Polyethylene glycol*, given orally *or* via nasogastric tube for 4– 6 hours (*or* until rectal effluents are clear) is indicated in: (a) poisoning with substances, not absorbed by activated charcoal, (b) cocaine/heroin

bowel stuffers, (c) toxic ingestion of enteric-coated or sustained release drugs, and (d) iron overdose.

Electrolyte imbalance due to large volume irrigation and catharsis is common during bowel irrigation, which must be prevented by regular monitoring and addition of adequate amount of electrolytes to irrigation fluids. Whole bowel irrigation is contraindicated in suspected bowel obstruction or perforation.

b. **Eyes decontamination** by immediate washing/irrigating them copious amount of saline or cold water is indicated in *splash-exposure* to organic solvents or hydrocarbons, detergents, alcohol, corrosives, etc. or *fume-exposures* to noxious gases. In severe exposures. Subsequent eye examination after fluorescein staining is advised for residual injury in these cases.

c. **Skin decontamination** with running-water wash or wet mopping after removal of all cloths, is indicated in contact-poisons, e.g. organophosphorus compounds *or* acid burns. Water should not be used for sodium *or* phosphorus exposure.

Special agents for skin decontamination include– Neosporin for super-glue, calcium gluconate for hydrofluoric acid, mineral oil for elemental sodium, etc.

Step IV. Elimination of absorbed toxins, involves measures to facilitate renal excretion as follows:

- **Forced diuresis** (IV Furosemide 1–2 mg/kg with large water intake), is of limited value as excretion of most toxins is not related to urinary volume and may lead to electrolyte disturbances.
- **Urinary pH modification** is more effective and safer method to enhance excretion of weak acidic/alkaline poisons, by keeping them in ionic stage within tubules to prevent reabsorption (*ion trapping*).

  Urinary alkalinization with sodium bicarbonate (1–2 ml/kg/dose to maintain urine pH 7.5–8.0) facilitates excretion of weak acidic substances, e.g. salicylates, phenobarbitone, etc.

  Urinary acidification with ammonium chloride (4 gm 2 hourly to maintain urine pH 5.5–6.5) facilitates excretion of weak alkaline substances, e.g. amphetamine, phenytoin and tricyclic antidepressants.
- **Hemodialysis/Hemoperfusion** is useful to eliminate dialyzable toxins, e.g. barbiturates, salicylates, theophylline, methanol, lithium, chloral hydrate, ammonia, isoniazid, thiocyanates, etc. However considering the risk of complications, it is recommended only in critically sick cases with heavy exposure and toxic blood levels. *Peritoneal dialysis* is of limited value. Dialysis is not useful in poisoning with digitalis, antihistamines, belladonna alkaloids and opiates.

Step V. Specific antidotes are available for many poisons, though effective only if given as early as possible within prescribed time-limits **(Table 27.27)**. Action-wise, these antidotes may be classified as – *physiological* (counteract physiological effects of poison), *chemical* (inactivate poison by combining them) or *physical* (prevent poison to reach the target organ).

TABLE 27.27: Specific antidotes for common poisoning

Anticholinergics	Physostigmine, Neostigmine*
Aluminium	Desferrioxamine*
Benzodiazepines	Flumazenil
β-blockers	Calcium gluconate, insulin+Glucose. Glucagon
Copper	Penicillamine
Cyanides	Na thiosulfate, Hydroxycobalamin Amyl nitrite*
Chloroform	N acetyl cysteine*
Digoxin	Antidigoxin Fab (antibody)
Ergot alkaloids	Sodium nitroprusside
Heavy metals[1]	Dimercaprol*, BAL
Hydrofluoric acid	Calcium gluconate, calcium chloride
Iron	Desferrioxamine, EDTA*
Insulin	Glucose
INH	Pyridoxine*
Irritant gases[2]	Oxygen, Budesonide*
Iodine	Sodium thiosulfate ?
Lead	DMSA, Dimercaprol, EDTA
Methemoglobinemia[3]	Methylene blue
Methanol	Ethanol, folic acid
Organophosphorus C.	Atropine, Pralidoxime (PAM)
Opioids	Naloxone
Paracetamol*	Acetylcysteine, Methionine
Phenothaizines	Diphenhydramine/diazepam
Phenol	Polyethylene glycol*
Phosphorus	Copper solution
Sympathomimetics	β-blockers
Theophylline	β-blockers
Cyclic antidepressants	Physostigmine, sodium bicarbonate
Warfarin	Clotting factor

*of questionable value. [1]arsenic, mercury, [2]carbon monoxide, Cyanide fumes, H_2S, others, [3]due to nitrites, nitrates; **C:** Compounds

Step VI. Supportive therapy: Frequent clinical and laboratory monitoring is essential in all poisonings, along with need-based supportive care, e.g.:

- Fluid and electrolyte correction,
- Oxygen and/or ventilatory assistance,
- Treatment of shock with volume-expansion (vasopressors are usually less effective),
- Control of seizures,
- Management of complications, e.g. cerebral edema, hyperpyrexia, hyper/hypoglycemia and infection.

Step VII. Laboratory diagnosis of exact poison and its blood levels is of limited use in clinical practice due to delayed availability of results. Further, drug levels may not correlate well with clinical severity. However, whenever possible, blood levels should be obtained in suspected poisoning for salicylates, anticonvulsant, digoxin and theophylline. While comprehensive toxin

TABLE 27.28: Preventive measures for childhood poisoning

- Safe storage of potentially toxic drugs/substances
  - Use of child-proof containers
  - Discarding the old/expired dated drugs
  - Storage of drugs/poisons in original containers
- Supervised drug administration
- Adequate parental supervision of child's activities
- Parental education before dispensing the drugs or chemicals
- Legal safety regulations
- Establishment of regional poisoning control centers

screening facility for multiple poisons (Panels) is available at many advanced centres, laboratory should always be informed about the clinical suspicion to narrow-down the search.

Step VIII. Secondary prevention with appropriate counselling is as important as the acute management of poisoning, to prevent recurrence of similar events. While complete psychiatric evaluation and legal formalities are essential in cases of intentional poisoning, parents of children with accidental poisoning should be counselled regarding basic safety-measures **(Table 27.28)**.

27.6.2 COMMON SPECIFIC POISONINGS

Some common poisonings in Indian children are as follows:

Hydrocarbon (Kerosene) poisoning: Hydrocarbon poisoning is the commonest cause of accidental poisoning and poison-related deaths in pre-school Indian children. Hydrocarbons include a large group of organic (e.g. petroleum distillates) and inorganic (e.g. turpentine or pine oil) substances.

Mechanism: Risk as well as manifestations of hydrocarbon poisoning depends on their volatility and viscosity. For toxicity considerations, hydrocarbons may be broadly divided into two groups:

a. *Low viscosity-high volatile* Aliphatic compounds, e.g. Kerosene and other petroleum distillates, turpentine, lubricants, etc., which carry high risk of aspiration;
b. *High viscosity-less volatile* Aromatic compounds, e.g. organic solvents, paints/paints remover, nail polish removers, etc., which are predominantly neurotoxic or hepatotoxic.

Some hydrocarbons, used as vehicle for pesticides or insecticides, have additional risks due to additives, e.g. organophosphorus compounds.

Kerosene, the commonest hydrocarbon associated with poisoning in India has been discussed in Ch 16.9.2.

Corrosive poisoning due to ingestion of household items containing acids or alkali, e.g. soaps and toilet cleaners are common in toddlers due to their inquisitive and exploratory nature.

Mechanism: Corrosives cause tissue injury on contact by a chemical reaction. Factors that determine the extent of injury include pH of the agent, quantity ingested and duration of contact with tissues, apart from other factors.

After exposure, corrosives initiate immediate inflammatory reactions at the site of contact, followed by tissue necrosis, leading to ulceration, sloughing and sometimes perforation, usually within 24–48 hours. While alkali ingestion leads to *liquefaction necrosis,* acids cause *coagulation necrosis.* In survivors, lesions heal over 2–3 weeks by fibrosis, leading to cicatrization and stricture formation.

Clinically, these cases present in three stages:

a. *Immediate burning pain* and swelling of the perioral region and oral cavity with drooling of saliva, dysphagia and epigastric pain, followed by,
b. *Secondary complication* due to internal tissue damage, e.g. hematemesis, esophagitis, mediastinitis or gut perforation.
c. After few weeks, child may present with dysphagia due to *secondary strictures.*

Immediate perioral reactions are more prominent in acid ingestion due to highly irritant nature of these chemicals. External lesions are usually mild in caustic or alkali poisoning, but often associated with more severe internal lesions and complications due to liquefaction necrosis.

Evaluation depends on the severity of disease and aims to detect internal complications. A baseline chest X-ray, including lateral film, is indicated in all cases, with neck and abdominal radiographs in selected cases. All cases with ingestion of large volume or concentrated products must undergo flexible endoscopy after 6–12 hours to detect internal lesions. Endoscopy is not needed in asymptomatic or mild cases and contraindicated in those with suspected perforation.

Management rests on the severity of event, time-lapsed since exposure and possibility of complications. Asymptomatic patient with history of minimal ingestion and no oropharyngeal burns may be discharged after few hours of observation.

Symptomatic cases with large volume ingestion require hospitalization, local decontamination by mouth wash, etc. and endoscopic examination at 12–24 hours to detect internal injury. Seriously sick cases may need intensive care.

Important steps in management include: (a) removal of residual chemical by generous wash, (b) protection of airway, including urgent endotracheal intubation in cases with respiratory and airway edema, (c) hemodynamic correction, and (d) supportive therapy for pain, nutrition, etc.

Attempts to dilute the ingested corrosive by encouraging oral water/milk intake are futile and use of emetics, neutralizing agents (acid for alkali poisoning and vice versa). Nasogastric aspiration is contraindicated

except after ingestion of chemicals with systemic toxicity, e.g. zinc chloride, or mixture with other poisonous substance, e.g. organophosphorus compounds.

Role of steroids to decrease airway edema or prevent stricture formation is controversial. Surgical gastrostomy may be required in cases with severe internal burns on endoscopy.

All cases with severe poisoning need repeat bronchoscopy after 3–4 weeks to detect the stricture formation and dilation if required.

Organophosphorus (OP) poisoning: OP poisoning is a major cause of intentional poisoning in adolescents, though most cases are accidental. OP compounds are ingredients of various insecticides/pesticides for domestic/agricultural use. and poisoning may develop after ingestion, inhalation or even contact with skin/mucus membranes, e.g. eyes.

Mechanism is the irreversible inhibition of enzyme *cholinesterase* – responsible for degradation of acetylcholine at post-synaptic sites, which leads to accumulation of acetylcholine and parasympathetic hyperactivity.

Clinical presentation depends on the type of individual OP compound as well as dose and route of exposure. Most cases manifest within few hours of ingestion with headache, weakness, blurred vision, giddiness and vomiting; followed by development of three well-defined symptom complexes with variable severity:

a. *CNS effects*, e.g. headache, giddiness, restlessness, ataxia, confusion, seizures, coma, etc.
b. *Nicotinic effects*, e.g. muscular fasciculations and weakness and even respiratory paralysis.
c. *Muscarinic effects*, e.g. Diaphoresis, Urinary incontinence, Miosis, Bradycardia/hypotension, Bronchospasm with/without pulmonary edema, *E*mesis, *L*acrimation and *S*alivation (*Pnemonic*s – DUMBBELS).

While muscarinic effects are prominent in early stages and with low-dose exposure, high-dose exposure predominantly presents with neurological and nicotinic effects. *Hyperglycemia without ketoacidosis* is common.

Diagnosis is largely based on history and clinical presentation with cholinergic toxidrome. It may be confirmed by low plasma *pseudocholinesterase* and/or RBC *acetylcholinesterase* enzyme levels, but severity of poisoning may not correlates with these levels.

Management: All patients with suspected OP exposure, even if asymptomatic, should be hospitalized as manifestations may develop even after 24–48 hours. Important steps in management include:

a. Immediate gastric lavage and skin/eye decontamination by irrigation with copious amount of water;
b. Appropriate resuscitative and supportive measures. Sedation, Tranquilizers and Theophylline should not be used in OP poisoning.
c. Specific antidotes, e.g. atropine and PAM, only in symptomatic cases.

Atropine is a physiological antidote for muscarinic effects of OP compounds with little effect on neural/nicotinic effects and should be started as soon as possible with a dose of IV 0.05–0.1 mg/kg, repeated every 10 minutes till full dilatation of pupils.

PAM (Pralidoxime) is the chemical antidote that dephosphorylates OP-cholinesterase complex to free some enzyme, provided given within 24-48 hours of exposure as IV 25-50 mg/kg over 10 minutes, followed by 5-10 mg 12-hourly (*or* 5 mg/kg/hour infusion). All patients should be observed for 48-72 hours after apparent recovery, as recurrence of respiratory or proximal muscular weakness is common. Some cases may develop OP-induced late peripheral neuropathy with predominantly distal muscle weakness for many months.

Opioids (Narcotics) poisoning: Opioids are natural or synthetic compounds with morphine-like activity, commonly used as pain-relievers in terminally sick persons or as *drug abuse*. Some common opioids include morphine, pethidine, codeine, heroin, pentazocine, etc.

Mechanism: On exposure via oral or IV route, these compounds interact with specific *opiate receptors* distributed throughout the body (specially brain), to produce central as well autonomic nervous system effects.

Clinically, Opioid toxicity presents with a characteristic *triad* of—(a) CNS depression, (b) respiratory depression, and (c) severe miosis, i.e. *Pin-point pupils*; along with other features, e.g. hypotension/bradycardia, constipation/paralytic ileus, vomiting, urinary retention and pruritis/bronchospasm due to histamine release. Aspiration, due to impaired gag reflex is common. Infants may present with seizures before development of CNS depression.

Management depends on severity and includes—(a) gut decontamination with gastric lavage and activated charcoal, (b) supportive care, and (c) specific antidote–*IV Naloxone 0.01–0.1 mg/kg*, which may be repeated as required *or* given as continuous infusion.

Opioid withdrawal, seen in chronic opioid dependence is uncommon in children and characterized by restlessness/insomnia, muscular twitching/seizures, excessive rhinorrhea/lacrimation/sweating and pupillary dilatation. Severe withdrawal may necessitate administration of a less potent opioid, e.g. methadone, followed by gradual tapering over 5–10 days.

Dhatura (Belladonna) poisoning: Accidental ingestion of the Dhatura seeds (Jimson weed) is not uncommon in Indian villages, though some cases may occur due to intentional ingestion or inhalation of Dhatura-smoke for hallucinogenic effect in adolescents.

Mechanism: Dhatura plant contains many belladonna alkaloids, e.g. atropine, scopolamine, hyoscyamine, etc.,

all strong anticholinergic agents with pronounced action of muscarinic receptors. Nicotinic receptors are less affected. Some of these alkaloids cross blood-brain barrier to cause neurological effects. Lethal dose for these alkaloids is ~4 mg.

Clinically, belladonna poisoning manifests within 30 minutes of exposure with:

a. *Peripheral anti-muscarinic effects*, e.g. excessive thirst (↓salivation), dry-red eyes (↓lacrimation), and dry/flushed skin (↓sweating). Severe cases may develop hyperpyrexia due to diminished sweating, diplopia due to symmetrical mydriasis, urinary retention, paralytic ileus and tachycardia/arrhythmia with mild hypertension.
b. *Central anti-muscarinic effects* begin with neuroexcitatory features, e.g. agitation, hallucinations, delirium, ataxia, tremors and seizures, followed by neurodepression after 1–2 hours, e.g. drowsiness or coma.

A case of Dhatura poisoning is often described as - hot as a hare, blind as a bat, dry as a bone, red as a beet and mad as a hen.

Management of Dhatura poisoning includes:

- Immediate gut decontamination by gastric lavage and activated charcoal,
- Supportive therapy for hyperpyrexia, dehydration, urinary retention, ileus, seizures, etc.,
- Specific antidote – *Physostigmine (0.02 mg/kg IV over 5–10 min)*, which needs to be repeated every 20 minutes. Antidote therapy is indicated only in severe neurological *or* cardiovascular toxicity.

Forced diuresis, urinary pH manipulation or dialysis have no role in belladonna poisoning.

Barbiturate poisoning: Phenobarbitone poisoning is more likely in epileptic children or those with other epileptic family member, due to easy availability of drug in the household.

Mechanism: Barbiturates act on Gamma aminobutyric acid (GABA) receptors to: (a) to reduce neuronal excitability, (b) block Na^+/K^+ channels, and (c) inhibit release of Calcium-dependent neurotransmitters. Serum phenobarbitone levels > 10 mg/dl are potentially lethal.

Clinically, these cases presents with dose-dependent severity of—(a) CNS depression, e.g. drowsiness or coma, (b) respiratory depression, and (c) hypotension and shock with/without renal failure. Bullous skin lesions, mimicking Steven-Johnson syndrome are seen in some cases.

Treatment is supportive with no specific antidote. Important measures include:

- Immediate gut decontamination by gastric lavage and activated charcoal;
- Forced alkaline diuresis with mannitol and $NaHCO_3$.
- Treatment of shock, ventilatory assistance and other supportive measures.
- Refractory cases may benefit from peritoneal/hemodialysis or hemoperfusion.

Naphthalene poisoning: Naphthalene balls are commonly used as moth-repellents and accidental ingestion is common in children. However, severe and even fatal toxicity has been reported in infants following prolonged dermal contact or inhalation exposure. Each ball usually weighs ~0.5–3.5 gm, while a dose as less as 0.25 gm may be fatal in infants/toddlers.

Mechanism: Naphthalene itself is an inert substance and toxic effects are caused by its body metabolite -naphthol, which leads to acute hemolysis and methemoglobinemia, specially in children with G6PD deficiency. Fatty meals before or after naphthalene ingestion increase severity of poisoning.

Clinically, most cases are asymptomatic, except GIT upsets, e.g. vomiting, abdominal pain and diarrhea for few days. However, *heavy* ingestion or co-existing G6PD deficiency may lead to acute hemolytic reaction after 24-48 hours with a triad of—(a) progressive anemia, (b) jaundice, and (c) dark-color urine; sometimes leading to acute renal failure.

Management: While gastric lavage is enough in most cases, large-quantity ingestion requires:

a. Immediate gastric lavage followed by active charcoal with cathartic administration,
b. Close monitoring for signs of hemolysis,
c. Treatment of severe hemolysis with plain/exchange blood transfusions and forced alkaline diuresis to prevent precipitation of hemoglobin in renal tubules.
d. *IV methylene blue* therapy (1–2 mg/kg slow infusion) in cases with persistent hypoxemia or methemoglobin levels >30%.
e. Exchange transfusion must be considered in cases with severe toxicity or those not responding to methylene blue therapy.

Phenothiazine poisoning: Phenothiazine poisoning, once very common, is rare at present due to declining use of these drugs as antiemetics. However, use of these agents, e.g. chlorpromazine, prochlorperazine or trifluoperazine in adult psychiatric disorders may cause accidental ingestion by household children.

Clinically, Phenothiazine toxicity may be dose-independent (*idiosyncratic*) or *dose-dependent*. *Idiosyncratic reactions* may develop even after therapeutic dose, presenting with extrapyramidal toxidrome, e.g. torticollis, oculogyric crisis, rigid twisting of body and speech/swallowing difficulties.

Although frightening in appearance, these cases respond dramatically to a single dose of IV/PO Diphenhydramine (1 mg/kg) or sedative, e.g. diazepam/promethazine. *Dose-dependent toxicity* presents with high

fever and neuro-excitation, e.g. agitation/delirium, seizures followed by coma, arrhythmia and shock. Miosis is common.

Some cases may develop *Neuroleptic malignant syndrome*—a potentially fatal state with hyperpyrexia, coma, extrapyramidal rigidity and circulatory instability. A simple urine test (Add 10 drops of Tinc. $FeCl_3$ in acidified urine sample > reddish-purple color indicates presence of phenothiazines in urine) may be used for bedside diagnosis.

Management of dose-dependent toxicity includes: (a) gut decontamination with gastric lavage and cathartics, and (b) supportive therapy for arrhythmia, shock, seizures, hyperthermia, etc.

Paracetamol poisoning: Although paracetamol is the safest antipyretic in therapeutic doses, a dose >140 mg/kg is potentially toxic. Young children are relatively more tolerant than adults to paracetamol overdosage.

Mechanism: Paracetamol toxicity is mediated by its intermediate hepatotoxic metabolite – *N-acetyl-p-benzo-quinoeimine* (NAPQI), which is rapidly deactivated by conjugation with glutathione. Paracetamol overdose leads to excess glutathione utilization and depletion, enabling free metabolite to cause hepatocellular damage.

Clinically, *hepatotoxicity* is the hallmark of paracetamol overdose and untreated course may be broadly divided into four stages:

a. *Acute stage* (1-24 hours) with nausea/vomiting, malaise, pallor and diaphoresis.
b. *Silent stage* (24-48 hours) with apparent recovery except mild tender hepatomegaly, abnormal liver function tests and oliguria.
c. *Stage of maximum liver damage* (48-96 hours) with reappearance of vomiting, progressive jaundice and peak liver function abnormalities. However, fulminant hepatic failure and death is rare in children (<1%). Some cases may develop acute renal failure.
d. *Stage of resolution* (4-14 days) with progressive and usually complete resolution of liver pathology in survivors.

Paracetamol toxicity is severe, if—(a) Plasma drug levels exceed 200, 100, 50 mg/dl at 4, 8 and 12 hours respectively,(b) Serum bilirubin or aspartate transaminase levels exceed 4 mg/dl *or* 1000 IU respectively, and (c) Prolonged prothrombin time at any stage.

Management includes:

a. Immediate gastric lavage followed by activated charcoal administration, and
b. *N-acetylcysteine* (NAC)—a precursor for glutathione synthesis, is the specific antidote for paracetamol poisoning that prevents hepatotoxicity by replenishing glutathione stores to inactivate NAPQI. It should be given as IV infusion 200 mg/kg (in 200–500 ml DW 5%) over 4 hours, followed by 100 mg/kg over next 16 hours. Maintenance dose of 100-200 mg/kg over another 16 hours may be repeated once again, if required.

   Oral NAC, though not as effective may be used if IV preparation is not available, given as 140 mg/kg loading dose > 70 mg/kg 4 hourly × 17 doses as 5% solution with soda or fruit juice). Since oral NAC is absorbed by activated charcoal, concurrent administration of both agents should be avoided.
c. *Methionine* (PO 2.5 gm 4 hourly × 4 doses) to replenish cellular glutathione, may be used as adjuvant in severe paracetamol toxicity.

Iron poisoning: Accidental ingestion of the large number of iron tablets is a common cause of drug-related poisoning in childhood. An elemental iron dose of ~60 mg/kg presents with serious toxicity, while a dose >300 mg/kg is potentially lethal.

Mechanism are—(a) direct corrosive effect on gut mucosa, (b) accumulation of free iron around mitochondria, leading to anaerobic metabolism and metabolic acidosis, (c) excessive production of free radicals, and (d) impaired coagulation.

Clinically, iron poisoning may present with five sequential stages with considerable overlapping:

a. *Acute stage* (½–2 hour), with vomiting, abdominal pain, GIT bleeding, and systemic manifestations, e.g. drowsiness, hyperventilation and hypotension.
b. *Stage of apparent recovery* (1–2 days),
c. *Stage of circulatory failure* with metabolic acidosis, coagulopathy and oliguria/anuria,
d. *Stage of hepatic failure,* usually a terminal event (2-4 days), and
e. *Stage of gastric scarring* (2-4 weeks) in survivors, which may present as chronic intestinal obstruction.

Management depends on expected dose of ingestion, assessed by history *or* free serum iron levels (> 50 µg/dl: possible, > 350 µg/dl: *definite*). Important steps in management include:

a. Gastric lavage with large-volume saline; 50–100 ml of $NaHCO_3$ solution must be left in the stomach after lavage to bind unabsorbed iron. Activated charcoal is of no value in iron poisoning while whole bowel irrigation is indicated only if large numbers of tablets are visible on skiagram.
b. *Supportive therapy* for acidosis, shock, etc.
c. *Chelation therapy* with IV Desferrioxamine (5–15 mg/kg/hour) is indicated only if serum iron levels >300 µg/dl and should be continued till the child continues to pass vinrose-color urine (due to iron-desferrioxamine complex).
d. Exchange transfusion is indicated only in refractory cases with serum iron >1000 µg/dl. Hemo/peritoneal dialysis has no role in iron poisoning.

Salicylate poisoning: While oral salicylates are rarely used in children at present, accidental ingestion or skin absorption from salicylate-containing rubefacient preparations is not uncommon.

Mechanism: Salicylates act as gastric irritant, inhibit many metabolic reactions, e.g. phosphorylation, *Kreb cycle*, aminoacid synthesis *and* decrease platelet adhesiveness. Potentially toxic dose is >150 mg/kg.

Clinically, these cases present with *three* stages:

a. Hyperventilation with respiratory alkalosis due to stimulation of respiratory centers, for ~6-12 hours;
b. Hypokalemia with paradoxical aciduria despite respiratory alkalosis due to compensatory loss of K^+ and H^+ ions in urine, lasting for 12–24 hours;
c. Progressive metabolic acidosis due to accumulation of lactic acid with dehydration and hypokalemia, after 12–24 hours.

First two stages may not be obvious in young infants *or* chronic salicylate poisoning.

Other common manifestations include vomiting/hematemesis, hypo/hyperglycemia and most cases die due to cerebral or pulmonary edema, hemorrhage, severe dyselectrolytemia or shock.

Serum salicylate levels after 6 hours of exposure (peak levels) are reliable indicators of severity – >50 mg/dl indicating toxicity and >90 mg/dl indicating severe toxicity. However, these levels are unreliable in chronic salicylate poisoning.

Management includes:

a. Immediate gastric lavage,
b. Supportive care with fluid/electrolyte and acid-base correction,
c. Urinary alkalinization with IV sodium bicarbonate (1–2 mEq/kg at 30 minutes interval for 4–6 hours).
d. Hemodialysis or hemoperfusion in severe cases with levels > 800 mg/dl.

Lead poisoning: Lead, a non-essential metal with no known physiological value, is ubiquitously present in human body due to environmental exposure. However, blood lead levels >10 µg/dl are potentially toxic.

Sources: Major source of lead-exposure in Indian children are—(a) inhalation of lead-containing vehicular/industrial emissions, (b) ingestion of lead-containing wall/toy paints usually as pica, or (c) water contamination due to use of old lead-coated pipes/containers. Industrial and vehicular pollution control measures have substantially reduced incidence of lead poisoning in recent years.

Mechanism: Primary toxicity of lead is due to its affinity for sulphydryl (SH) group of proteins, present in metabolic enzymes – specially those required for heme synthesis. Irreversible binding of lead to this group leads to impaired heme synthesis as well as accumulation of proximal metabolites, responsible for toxic effects.

Clinically, lead poisoning may be *acute* or *chronic*, though acute lead poisoning is rare at present.

Acute lead poisoning presents with—(a) acute abdominal colic mimicking surgical emergencies, (b) acute encephalopathy with seizures and coma, (c) severe anemia, and (d) peripheral neuropathy, over a period of few days.

Chronic lead poisoning is related to blood lead levels and may be subclinical at lower levels. Important manifestations of chronic lead poisoning include:

- Recurrent abdominal pain with constipation, anorexia and metallic taste in mouth;
- Microcytic hypochromic anemia, with basophilic stippling of RBCs;
- Progressive lead encephalopathy with headache, irritability and impaired cognitive functions, followed by ataxia, seizures and coma in severe cases;
- Other manifestations, e.g. blue lines over gums, renal rickets due to Fanconi-like syndrome or peripheral neuropathy.

Management depends on presence of symptoms and blood lead levels (BLL) and includes: (a) elimination of the potential source of exposure, (b) supportive therapy for encephalopathy, etc. and (c) chelation therapy as follows:

- **BLL <45 µg/dl:** *No chelation therapy* is required irrespective of age, though attempt should be made to identify and remove the source of exposure, followed by revaluation after 2-4 weeks in borderline cases.
- **BLL 45-69 µg/dl:** *Oral chelation therapy* is indicated in: (a) all children <10 years, (b) all girls >10 years, and (c) symptomatic boys >10 years, preferably using Succimer or DMSA (PO 350 mg/m^2/dose 8-hourly for 5 days, then 12 hourly for next 14 days). Penicillamine may also be used to treat these cases (25–30 mg/kg/day for 10–14 days), but with higher risk of side-effects.
- **BLL >70 µg/dl:** *Oral or parenteral chelation therapy* is recommended in all cases irrespective of age or symptoms. *Parenteral chelation therapy* with urgent hospitalization is essential in all cases with severe neurological symptoms or encephalopathy with Dimercapol (IV 75 mg/m^2/dose 4-hourly till BLL drops < 60 mg/dl) *or* Calcium disodium edentate or EDTA (IV 1000 mg/m^2/day for 5 days).

27.7 SUDDEN INFANT DEATH SYNDROME

Sudden infant death syndrome is defined as *"the unexpected death of an infant (<1 year), the cause of which remains unexplained after an autopsy, death scene investigation and review of case history"*. Thus, the unexplained etiology despite best efforts is the hallmark of SIDS.

While incidence of SIDS has declined in recent years, it continues to be an important cause of infant mortality

TABLE 27.29: Risk factors for SIDS

- **Family history of SIDS**
- **History of acute life threatening events***
- **Infant-related**
  - Age (90% cases in 1–6 months group)
  - Prematurity
  - Male gender
  - Recent febrile illness
  - Tendency to sleep in prone position
- **Maternal factors:**
  - Young, undernourished or ill mothers
  - Unwed mothers
  - Repeated pregnancy at short intervals
  - Smoking or substance abuse
- **Environmental factors:**
  - Low socioeconomic status
  - Winter season
  - Use of soft-bedding

*discussed later

in developed countries with an estimated incidence of ~ 0.7/1000 live births.

Risk factors: Most of these deaths occur during first 6 months of life in previously healthy infants, usually during sleep at night and in winter season **(Table 27.29)**.

Pathophysiology of SIDS is still obscure, though seems to revolve around the *maturational delay or pathological abnormalities in cardiorespiratory regulation* during sleep, due to:

- Impaired brain-stem arousal response to sleep-related asphyxia,
- Impaired chemoreceptor sensitivity to hypercarbia or hypoxia,
- Impaired respiratory response, e.g. prolonged periodic breathing
- Impaired heart-rate variations or arrhythmias during sleep, ? due to decreased vagal tone,
- Autonomic dysfunction in response to temperature changes during sleep.

Management: As SIDS is a fatal event, management involves: (a) parental counseling, specially to remove their guilt, (b) detailed review of previous health records and autopsy findings to exclude identifiable causes of death or epidemiological risk factors, (c) prospective care during next pregnancy with elimination of high-risk factors.

A simple intervention, e.g. campaign to avoid prone position during sleep has reduced incidence of SIDS in United States by ~ 50%.

Acute life-threatening events (ALTS) or *near-missed* SIDS, are defined as "*an un-expected and frightening change in infants' behavior, characterized by apnea, color change, limpness and choking*". These events are more common than SIDS (0.5–1/1000 live births) and cause is identifiable in ~50% of these cases after detailed investigations **(Table 27.30)**. However, an infant with

TABLE 27.30: Causes of ALTS

- ***Idiopathic*** (50%)
- ***Cardiac:*** CHDs, long-QTc syndrome, arrhythmia
- ***Resp.:*** GER, airway anomalies, chronic lung disease
- ***CNS:*** Seizure disorder, brain-stem lesions
- ***Metabolic:*** Hypoglycemia, IEM*
- ***Infections:*** Acute fulminant sepsis, meningitis
- ***Trauma*** to vital organs e.g. head injury

***GER:** Gastro-esophageal reflux; **IEM:** Inborn errors of metabolism; e.g. carnitine deficiency, urea cycle defects and fatty acid disorders

ALTS carries 3–5 times higher risk of subsequent SIDS and needs to be investigated and treated for identifiable cause with follow-up in early childhood.

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CHAPTER

28

Social Pediatrics

Mukesh Agrawal

India, the seventh largest country in the world, is the most populous country in the world. While occupying only 2.6% of world area (3287263 km^2), it sustains 17.8% of global population (1428 million) with an overall population density of 481/km^2. Uttar Pradesh, Maharashtra and Bihar are the three most populous states of India, in this order. Some important demographic characteristics of India are given in **Table 28.1**.

28.1 NATIONAL HEALTH OBJECTIVES

Large population, poverty, illiteracy and inadequate sanitation have been identified as key factors for poor population health and inadequate health infrastructure in developing countries, including India.

Consequently, many novel strategies have been designed and implemented since independence to overcome these barriers and uplift general health status of Indian population, with special emphasis on high-risk groups, e.g. woman and children. Some important national objectives and targets related to population health in general and children's health in particular, are as follows:

TABLE 28.1: Demographic profile of India

Crude birth rate	19.5
Crude death rate	6.0
Natural growth rate	13.5
Total fertility rate	2.0
Population distribution (<19 yrs)	35.0 %
0-4 yr	7.5%
5-9 yr	8.3%
10-14 yr	9.0%
15-19 yr	10.2%
Male:female ratio	1000:1020*
Male female ratio at birth	1000: 929*
Literacy rate (male/female)	84.4%/ 71.5%*
Life expectancy (2020)	70.8 (69.5/ 72.2)

Source: SRS report 2022 (Ref 2020 data), * NFHS- 2021 (Ref 2019-21 data)

Sustainable development goals (SDGs): Encouraged by the major achievements under millenium development goals (MDG), UN has proposed 17 SDGs for further international development to be achieved by the year 2030. Of these, Goal # 3, i.e. *to ensure healthy lives and promote well-being for all at all ages*, includes three important targets directly related to mother and child health, as follows:

- To reduce the global maternal mortality ratio < 70/ Lac live births.
- To end preventable deaths of newborns and under-5 children, with Neonatal mortality rate <12/1000 live births and Under-5 Mortality < 25/1000 live births.
- To end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and to combat hepatitis, water-borne diseases and other communicable diseases.

National Health Policy (2017) following the previous policies of 1983 and 2002, aims to achieve universal health coverage and delivering quality health care services to all at affordable costs with following objectives:

- Improving the general life expectancy with healthy life and sustain healthy life
- Reduce the mortality, specially in newborns, infants and under-five children
- Reduce the prevalence/incidence of selected diseases
- Improve coverage, finances and performance of health System
- Strengthen health infrastructure and information/ management system.

Certain specific health goals and targets have been established under this policy, to be achieved in time-bound manner, some of whom are related to child health as enlisted in **Table 28.2**.

28.2 CHILD HEALTH INDICATORS IN INDIA

Knowledge of the vital statistics or health indicators in a population is important not only to know the present

TABLE 28.2: National Health Policy 2017 (Targets and Year of Achievement)

Indicator	*Target*	*Year**
Mortality indicators		
IMR	28	2019
Under-5 MR	23	2025
MMR	100	2020
NMR	16	2025
SBR	Single digit	2020
Disease elimination/control		
HIV	90:90:90*	2020
Malaria (Incidence)	<1: 1000	2020
Leprosy elimination	<1: 10000	2018
Kala-azar elimination	<1: 10000	2017
Filaria elimination	<1% Mf	2017
TB cure rate/elimination	85%	2025
Stunting (Under-5)	Reduce by 40%	2025
Health services coverage		
ANC visits (>4) visits	90%	2025
Safe delivery	90%	2025
Infant immunization	90%	2025
Safe water/sanitation	100%	2020
Increase health budget	2.5%	2025

*90% PLHA know their HIV status, 90% receive sustained antiretroviral therapy and 90% on antiretroviral therapy have viral suppression.

TABLE 28.3: Current status of child health determinants in India

Mortality indicators (SRS 2022)*	
Infant mortality rate	28
Perinatal mortality rate (PNR)	18
Stillbirth rate	3
Neonatal mortality rate (NMR)	20
Early neonatal mortality rate	15
Late neonatal mortality rate	5
Post-neonatal mortality rate (PNMR)	8
Under-five mortality rate (U5MR)	32
Maternal mortality rate (MMR/Lakh)	99
Antenatal care (NFHS-5,2021)**	
Adequate (Minimum 4) ANC visits	58.1%
Iron-folic supplements for 100 days	44.1%
Tetanus immunization	92.0%
Perinatal care (NFHS-5,2021)**	
Institutional deliveries	88.6%
Unsafe deliveries	10.6%
LSCS deliveries	21.5%
% LBW	18%
Infant feeding practices (NFHS-5, 2021)**	
Early breastfeeding (within <1 hour)	41.8%
Exclusive breastfeeding till 6 months	63.7%
Initiation of complementary feeds @ 6 months	45.9%
Adequate Diet in breastfed (6–23 months)	11.1%
Adequate Diet in non-breastfed (6–23 months)	12.7%
Immunization coverage (NFHS-5, 2021)**	
Fully immunized (till 23 months)	76.4%
BCG	95.2%
DPT/Penta vaccine	86.7%
OPV	80.5%
Measles 1	87.9%
MMR	31.9%
RV	36.4%
Vitamin A supplement in last 6 months	71.2%
Health care utilization	
% ARI cases visiting health care facility	69.0%
% Diarrhea visiting health care facility	68.9%
% use of ORS in diarrhea	60.6%
% use of Zinc in diarrhea	30.5%

source: *SRS Statistical report 2022 (reference 2020 data)
**NFHS-5 Fact sheet 2021 (reference 2019-21 data)

status but also to: (a) comparing the health status of two different populations, (b) assess the effectiveness of socioeconomic and cultural changes in a population as well as effectiveness of health interventions, and (c) identify the need for further high priority areas, requiring attention

Two most reliable sources of health indicators in India are: (a) National Family Health Surveys (NFHS) conducted country-wide every 5-7 years; and Sample Registration Surveys (SRS) conduced periodically in a pre-defined sample. **Table 28.3** provides current status of some important health indicators related to child health in India.

Some important national health indicators are as follows:

Infant mortality rate (IMR) is considered as the most reliable indicator of child health and MCH care in the community.

Definition: IMR is defined as "*the ratio of deaths registered in a given year to the total number of live births*", expressed as a rate per 1000 live births, i.e.

IMR = Total deaths <1 year of age/Total live births × 1000.

Current status: Current IMR in India is estimated to be 28/1000 live births (SRS 2020) or 35.2 (NFHS-5 2019–21), as compared to the 5-8/1000 in developed countries. Within the country too, IMR varies from state to state and in urban vs. rural population due to socioeconomic and healthcare factors. IMR is lowest Puducherry and Kerala, moderate in Maharashtra and highest in Bihar and Chhattisgarh **(Table 28.4)**.

TABLE 28.4: States-wise distribution of key mortality indicators*

	IMR	*NMR*	*UNDER-5 MR*
Andhra Pradesh	30.3	19.9	35.2
Andaman and Nicobar	20.6	12.3	24.5
Arunachal Pradesh	12.9	7.7	18.8
Assam	31.9	22.5	39.1
Bihar	46.8	34.5	56.4
Chandigarh	NA	NA	NA
Chhattisgarh	44.3	32.4	50.4
Dadar and Nagar Haveli	31.8	21.4	37.0
Delhi	24.5	17.5	30.6
Goa	5.6	5.6	10.6
Gujarat	31.2	21.8	37.6
Haryana	33.3	21.6	38.7
Himachal Pradesh	25.6	20.5	28.9
Jammu and Kashmir	16.3	9.8	18.5
Jharkhand	37.9	28.2	45.4
Karnataka	25.4	15.8	29.5
Kerala	4.4	3.4	5.2
Lakshadweep	NA	NA	NA
Ladakh	20.0	11.4	29.5
Madhya Pradesh	41.3	29.0	49.2
Maharashtra	23.2	16.5	28.0
Manipur	25.0	17.2	30.0
Meghalaya	32.3	19.8	40.0
Mizoram	21.3	11.4	24.0
Nagaland	23.4	10.2	33.0
Odisha	36.3	27.0	41.1
Punjab	28.0	21.8	32.7
Puducherry	2.9	2.3	3.9
Rajasthan	30.3	20.2	37.6
Sikkim	11.2	5.0	11.2
Tamil Nadu	18.6	12.7	22.3
Telangana	26.4	16.8	29.4
Tripura	37.6	22.9	43.3
Uttarakhand	39.1	32.4	45.6
Uttar Pradesh	50.4	35.7	59.8
West Bengal	22.0	15.5	25.4
All India	**35.2**	**24.9**	**41.9**

**Source:* NFHS-5 Fact sheet 2021 (reference 2019-21 data)

Infancy includes two crucial periods of human life-neonatal period and post-neonatal period. IMR denotes a sum total of *Neonatal mortality rate* or NMR, i.e. deaths <28 days and *Post-neonatal mortality* rate or PNMR, i.e. deaths from 28 days 1 year (Ch 1.1). Analysis of data reveals that NMR accounts for > 70% of deaths in infancy. Interestingly, NMR is higher in males (? biologically fragile sex), while PNMR is higher in females due to sociocultural neglect.

TABLE 28.5: Major causes of infant mortality in India

- **Neonatal period**
  - Low birth weight and prematurity
  - Birth asphyxia
  - Congenital malformations
  - Perinatal and neonatal infections
  - *Others:* HDN, placental malformations
- **Post-neonatal period**
  - Acute respiratory infections
  - Diarrheal disorders
  - Vaccine preventable diseases, e.g. measles
  - Malnutrition
  - *Others:* Accidents, congenital malformations

HDN: Hemolytic disease of newborn

Causes: Leading causes of infant mortality vary in neonatal and postneonatal period **(Table 28.5)**. According to SRS report on causes of deaths 2017-2019, *neonatal problems* (53%), *pneumonia* (17%), *diarrheal disease* (5%) and other *severe infections* (4%) are leading cases of IMR in Indian children.

While most neonatal deaths are due to endogenous factors, e.g. prematurity, birth asphyxia and congenital malformations; majority of post-neonatal deaths may be attributed to exogenous factors, e.g. infection and nutrition. As most of these post-neonatal deaths are preventable, the sharp decline in IMR during last century in India (204 in 1911 to 58 in 2006) is predominantly due to decline in PNMR (preventable), rather than NMR (difficult to prevent).

Determinants: Infant mortality is multi-factorial in origin, affected by various biological, socioeconomic and environmental factors. Some important high-risk factors for IMR include:

- *Biological factors:* Low birth weight, maternal age <19 years or >30 years, first-born child, repeated pregnancies (>3rd birth order), short birth spacing (<1 year), etc.
- *Socioeconomic factors:* poverty, large family size, maternal illiteracy, girl child, illegitimate pregnancies, top feeding or other harmful customs/practices, etc.
- *Environmental factors*: overcrowding, lack of safe water supply, poor excreta disposal and hygiene, etc.
- *Healthcare factors*: unattended/untrained deliveries, inadequate perinatal care, poor immunization coverage, limited health care and IEC activities, specially in rural regions, etc.

Interventional strategies: A multi-pronged approach is essential to reduce IMR in a given population, comprising following main measures:

- *General measures:*
  - Socioeconomic development of community
  - Improvement in environmental sanitation

  - Promotion of female literacy
  - Preconception family planning
- *Specific measures:*
  - Antenatal care
  - Deliveries by trained birth attendants
  - Breastfeeding
  - Immunization for vaccine preventable diseases
  - Growth monitoring and promotional activities
  - Promotion of oral rehydration therapy
  - Early diagnosis and treatment of illnesses
- *Strengthening of primary health care* to manage common problems and identify at-risk cases for referral.

Under-5 mortality rate (child mortality rate) is considered as the best single indicator of overall socioeconomic development and well-being of the community, as majority of its causes, e.g. malnutrition and infection are dependent on the socio-economic status, environmental hygiene and health awareness in the population.

Internationally, child mortality rate is defined as the *annual deaths <5 years of age (IMR included) out of per 1000 live births in the same year.* However, in India, it calculated as annual deaths <5 years of age out of per 1000 under-5 children.

In India, Under-5 mortality has shown exemplary decline in last few decades (242 in 1960 to 32 in 2020 as per SRS or 41.9 as per NFHS-5), largely due to decline in IMR and reduction in vaccine-preventable deaths.

Leading cause of childhood mortality beyond infancy include Injuries (218%), Pneumonia (18%), non-communicable diseases (14%) and diarrheal diseases 13%. (SRS-COD report 2017-19)

Two other important child health indicators *Neonatal Mortality rate (NMR) or Perinatal Mortality rate (PNR)* have been discussed in **Ch 12.2.**

28.3 NATIONAL HEALTH PROGRAMMES

Since independence, many national health programmes, targeted to improve the child health have been launched time to time, according to contemporary needs, priorities and feasibility. Many of these programs have since been discontinued or amalgamated with others, to avoid duplication of efforts and wastage of scarce resources.

28.3.1 NATIONAL HEALTH MISSION

National Health Mission is the flagship public health program of Government of India, launched in may 2013 by incorporating Previous *National Rural Health Mission* (NRHM) as one sub-mission of the program and launching a new *National Urban Health Mission* (NUHM) as another sub-mission.

National Rural Health Mission (NRHM) was launched in 2005, to provide equitable, affordable and quality health care to the rural population, especially the vulnerable groups. Cities and towns with population below 50,000 persons are covered under NRHM. It also attempted to integrate various vertical national health programs, e.g. Reproductive and child health program, National vector borne disease control program, etc. An *Accredited Social Health Activist* (ASHA) – local resident women with some formal education, communication skills and leadership qualities is the key field person for NRHM interventions.

National Urban Health Mission (NUHM): NUHM seeks to improve the health status of the urban population particularly slum dwellers and other vulnerable sections by facilitating their access to quality primary health care. NUHM would cover all state capitals, district headquarters and other cities/towns with a population of >50,000 persons in phased manner. ASHA remains the link worker in NUHM as well.

Some important national health programs **(Table 28.6)**, operative at present, are discussed in this section, while others have been discussed in related chapters.

TABLE 28.6: Important national health programs related to children

- **Reproductive, Maternal, Newborn, Child and Adolescent Heath (RMNCH+A) Strategy**
- **Integrated Management of Neonatal and Childhood Illnesses (IMNCI)**
- **General child health programs**
  - Integrated Child Development Scheme (ICDS)
  - Rashtriya Bal Swasthya Karyakram (RBSK)
  - Navjaat Shishu Suraksha Karyakram (NSSK)
  - India Newborn Action Plan (INAP)
  - Janani Shishu Suraksha Karyakaram (JSSK)
  - Home based Newborn Care (HBNC)
  - Rashtriya Kishor Swasthya Karyakram (RKSK)
- **Nutritional support programs**
  - General nutrition
    - Mid-day Meal Scheme
    - POSHAN Abhiyaan
  - Nutrient-Specific
    - National Prophylaxis Programme for Prevention of Nutritional Blindness
    - National Iron Plus Initiative (NIPI), Anemia Mukt Bharat
    - National Iodine Deficiency Disorders Control Programme
- **Immunization programs**
  - Universal Immunization Program (UIP)
  - Mission Indradhanush
  - Pulse Polio Immunization
- **Disease-specific programs**
  - National Vector Borne Diseases Control Programme (NVBDCP)
  - National Control of Diarrheal Diseases Programme
  - National Acute Respiratory Infection Control Programme
  - National Tuberculosis Elimination Programme (NTEP)
  - National Leprosy Eradication Programme
  - National AIDS Control Programme (NACO)
- **Miscellaneous programs**
  - Under-Fives' clinic
  - Child Guidance clinic
  - School health Service

28.3.2 REPRODUCTIVE, MATERNAL, NEWBORN, CHILD AND ADOLESCENT HEALTH (RMNCH+A) APPROACH

In February 2013, Government of India launched a strategic approach to Reproductive, Maternal, Newborn Child and Adolescent Heath (RMNCH+A), which has become the heart of the India's flagship public health program, the *National health mission (NHM)*.

RNMCH+A is a paradigm shift from previous RCH programs, recognizing the need to include adolescents as a distinct life-stage in the holistic approach.

Objectives: RMNCH+A strategy aims to achieve various NHM goals revised time to time, also specified in national health policy 2017 **(Table 28.2)**. It also aims to focus on reducing maternal, newborn and child mortality as per SDG Goal 3 for 2030, i.e. reduction in: (a) MMR <70/1000 and (c) NMR <12/1000 live births and U5MR <25/1000 live births.

Components: RMNCH+A strategy rests on the provision of comprehensive care in five pillars of MCH services, i.e. Reproductive, Maternal, Neonatal, Child and Adolescent health, with plus (+) sign representing: (a) addition of adolescent health, (b) linkage of MCH services with reproductive health, (c) linkage of community-based services to facility-based care, and (d) linkage between various levels of health facilities from primary health centres to tertiary hospitals.

Interventions: Table 28.7 summarizes important interventions under RMNCH+A, often termed as *5 × 5 matrix* (*Five* high impact interventions in *Five* components), along with other measures, e.g. strengthening of health system and monitoring, prioritization of high-impact interventions in different life-cycle stages and intersectoral coordination.

These interventions, also termed as *continuum of care*, cover *Five* phases of life-cycle, i.e. adolescence, pregnancy, birth, newborn and childhood, and different levels of health care. Strategy also involves *Five* intersectoral interventions-Water, Sanitation, Nutrition, Education and Empowerment.

Implementation: RMNCH+A is not a health program *per se* but a guiding strategy to cover different aspects of care under different programs, e.g. JSSK, RBSK, NSSK, UIP, etc. discussed later.

RCH portal is designed for early identification and tracking of the individual beneficiary throughout the reproductive lifecycle of women and promote, monitor and support the reproductive, maternal, new-born and child health (RMNCH) schemes/programme delivery and reporting.

This portal helps health workers to (a) monitoring implementation of health schemes, (b) plan for service delivery and identification of beneficiary for antenatal Check-up, postnatal Check-up and Immunization Services, (c) Identification of high-risk pregnant women and tracking their health conditions and assistance during the delivery, (d) generate the work plan for delivery of immunization services to children.

TABLE 28.7: Important components of RMNCH+A strategy

A. Reproductive health
1. *Birth-spacing:* Postpartum and interval IUCDs
2. Reproductive traction infection case-management
3. Home delivery of contraceptives
4. Comprehensive abortion care and pregnancy-testing kit
5. Quality sterilization services
B. Maternal health
1. Pregnancy registration and quality antenatal care
2. High-risk screening of pregnant mothers
3. Skilled obstetric care at all delivery points
4. Review of maternal/infant deaths for corrective actions
5. Post-partum sterilization
C. Newborn health
1. Early and exclusive breastfeeding
2. Home-based newborn care
3. Essential newborn care and resuscitation
4. Care of sick newborn: SNCU, NBSU, etc.
5. Community-level use of gentamycin
D. Child health
1. *Nutrition care:* IYCF with micronutrient supplementation
2. *Facility- based IMNCI:* sp for diarrhea and pneumonia
3. Care of severe acute malnutrition (NRCs)
4. Universal immunization
5. Screening for 4 D's (RBSK)
E. Adolescent health
1. Address teenage pregnancy and contraceptive use
2. Community-based information and counseling services
3. *Facility-based service:* ARSH clinics
4. National iron-plus initiative
5. Promote menstrual hygiene

IUCD: Intrauterine Contraceptive Devices; **IYCF:** Infant and Young Child Feeding; **IMNCI:** Integrated Management of Neonatal and Childhood Illnesses; **NRC:** Nutritional Rehabilitation Centres; **RBSK:** Rashtriya Bal Suraksha Karyakram; **ARSH:** Adolescent Reproductive and Sexual Health Clinics.

28.3.3 INTEGRATED CHILD DEVELOPMENT SERVICES (ICDS)

Integrated child development services (ICDS), launched on 2nd October, 1975, is the earliest comprehensive national health program, which targets *holistic development* of the child and uses an *integrated approach* to provide basic services for better child care.

Objectives of ICDS are to:

- *Improve* nutritional and health status of children < 6 years.
- *Ensure* proper physical, psychological and social development.
- *Reduce* mortality, morbidity, PEM and school dropouts.

TABLE 28.8: Components of ICDS

Components	*Child <6 year*	*P/L women*
• Supplementary nutrition	yes	yes
• Immunization	yes	yes (TT)
• Health check-up	yes	yes*
• Referral services	yes	yes
• Nutrition/health education	–	yes
• Non-formal education	(3–6 years)	–

P/L: Pregnant and lactating mothers
*Health check-up is provided to all women in reproductive age group (15–44 years), irrespective of pregnancy/lactation status.

- *Co-ordinate* amongst various departments in child health programs.
- *Enhance* mother's capability to look after her child's needs through proper nutrition and health education.

Beneficiaries of the program are: (a) children <6 years, and (b) women in reproductive age (15–44 years).

Components/services: *Six* basic services offered under ICDS are enlisted in **Table 28.8**. In addition, an additional component, i.e. Adolescent girls scheme (*Kishori Shakti Yojana*) has been included subsequently in selected ICDS blocks, to provide health education, literacy, recreation and skill development services for school drop-out girls (11–18 years age).

Some important services are as follows:

- **Supplementary nutrition** is provided to all under-6 children, adolescent females and pregnant/lactating (P/L) mothers, using locally available and acceptable hot cooked/ready-to-eat foods. It aims to provide *500 cal with 12-15 gm proteins for 1–6 years children;* 600 cal with 18-20 gm proteins to pregnant, lactating (P/L) or adolescent females; and 800 cal with 20-25 gm proteins to severely malnourished children, for minimum 300 days in a year. Other activities under supplementary nutrition are: (a) vitamin A prophylaxis to <6 children, (b) iron folic acid supplementation to P/L mothers and children, and (c) promotion of iodized salt usage.
- **Immunization** is provided to children and pregnant mothers as per national immunization schedule and anganwadi workers maintain immunization records of all beneficiaries.
- **Health check-up** services for children include-regular weight and development monitoring, early diagnosis/referral/treatment of minor illnesses with simple medications, e.g. PEM, diarrhea, acute respiratory infections, etc. and periodic deworming.

  For P/L mothers, regular antenatal checkups are provided at anganwadi centers. These services are provided by local primary health centre/subcentre staff, e.g. ANMs.
- **Nutritional/health education** under ICDS aims to enhance capability of women in reproductive age group to look-after their own as well as their children's health and nutritional needs. Important components of this education, rendered via group sessions, home visits and demonstrations, include-promotion of breast feeding, family planning, safe hygiene and health-service utilization.
- **Non-formal education** (early childhood care and preschool education) is the back-bone of ICDS, a strategy to enhance its utilization and facilitate total development of child through early stimulation.
- ***Referral services*** based on IMNCI and other relevant guidelines.

Operational aspects: ICDS is a multi-sector program, under the primary responsibility of Department of Women and Child Welfare, Ministry of Human Resources, Government of India. Project is implemented under block-wise administrative units of three types (tribal, rural and urban slum blocks).

Each urban or rural block serves ~1,00,000 population, while a tribal block caters to ~35,000 population. Currently, over 5500 blocks are operational under this scheme.

Anganwadi centers, one per 1000 population, is the most peripheral service center under ICDS scheme, looked after by a local trained women, designated as *Anganwadi worker*. Each ICDS block is headed by *child development project officer* (CDPO), supported by medical officer of local health center and other personnel.

Entire expenditure of this scheme is borne by central and state government in 60:40 ratio, while supplementary nutrition component id funded by both as 50:50.

Review Periodic reviews of ICDS projects have shown distinct superiority and benefits on child health indicators over those in Non-ICDS areas. Hence, future thrust is not only directed to expand population coverage, but also to use large network of anganwadi centers and workers as an out-reach point for other national programs.

28.3.4 RASHTRIYA BAL SWASTHYA KARYAKRAM (RBSK)

Rashtriya Bal Swasthya Karyakram (RBSK), launched in 2013, aims for early detection and intervention for 4 Ds, viz. Defects (birth), Deficiencies, Diseases, Development delays including disability, specially in children aged 0-6 years.

Coverage: Total 30 conditions have been covered under this scheme for screening, early detection and intervention in children below 18 years **(Table 28.9)**. In addition, states may add other conditions based on the local prevalence, e.g. sickle cell disease or goiter.

Components of this program include:

- *Facility-based screening* of newborns in institutional deliveries, by existing health-staff.
- *Community-based screening* of newborns by home visits by ASHA, till 42 days of age.

TABLE 28.9: Health conditions screened under RBSK

Defects at birth	*Deficiency disorders*
1. Neural tube defects 2. Down syndrome 3. Cleft lip/palate 4. Club foot (CTEV) 5. Dev. dysplasia of hip 6. Congenital cataract 7. Congenital deafness 8. Congenital heart disease 9. Retinopathy of prematurity	10. Anemia (Severe anemia) 11. Bitot's spots (Vit A def) 12. Rickets (Vit D Def) 13. Severe acute malnutrition 14. Goitre
Childhood diseases	***Developmental delay and disabilities***
15. Skin conditions, e.g. scabies 16. Otitis media 17. Rheumatic heart disease 18. Reactive airway disease 19. Dental caries 20. Convulsive disorders	21. Vision impairment 22. Hearing impairment 23. Neuromotor impairment 24. Motor delay 25. Cognitive delay 26. Language delay 27. Behavioral disorder (Autism) 28. Learning disorders 29. Attention deficit disorders 30. Cong hypothyroidism, Sickle cell anemia, Thalassemia*

- *Anganwadi-center based screening* of children from 6 weeks to 6 years, by dedicated mobile teams.
- *School-based screening* for school children by dedicated mobile teams.

Implementation: RBSK envisages:

- Screening of all under-6 children in the community at different screening points, e.g. home, anganwadis or schools, by mobile health teams, at least twice a year;
- Establishment of ***District Early intervention centers*** (DEIC), funded under NHM, for screening and diagnostic assessment, domain-specific management, referral services to specialists, and Follow-up care.

While RBSK primarily target children aged 0-6 years, DEIC also provides referral services to older children for surgery and rehabilitation.

28.3.5 NAVJAAT SHISHU SURAKSHA KARYAKRAM (NSSK)

Navjaat Shishu Suraksha Karyakram (NSSK), launched in 2009, aims to train health personnel in the Basic Newborn Care and Resuscitation with updated algorithms and technology, to improve neonatal survival.

Objective of this program is to ensure presence of a trained health person at every delivery point, in simple life-saving issues, e.g. prevention of hypothermia, prevention of infection, early initiation of breastfeeding and basic newborn resuscitation. NSSK aimed to train all health workers and doctors involved in delivery and newborn care.

Implementation: Presently, NSSK is a training package with two days classroom and hands-on training, including supply of a resource manual. NSSK Manual 2020* provides detailed action plan for logistics, methodology and agenda for this training, apart from standard guidelines to prevent, identify, and manage life-saving issues in newborn care, starting from the preparation of delivery room to the transport of high-risk newborns for higher centres.

**available at...https://nhm.gov.in/index1.php?lang=1andlevel=1andsublinkid=1427andlid=781.*

28.3.6 INDIA NEWBORN ACTION PLAN (INAP)

India Newborn Action Plan (INAP), launched in 2014 in response to Global "*Every Newborn Action plan (ENAP)*", is a strategy to reduce the preventable newborn deaths and still-births.

Objectives: INAP aims to achieve a "*Single-digit Neonatal Mortality Rate and Single-digit Stillbirth Rate by 2030*".

Components: INAP is implemented within the RMNCH + A framework with 6 major components:

a. ***Pre-conception and Antenatal care*** including adolescent friendly health services, reproductive health and family planning, antenatal care and counseling for birth-preparedness.
b. ***Care during labour and child-birth,*** by safe-delivery practices, timely referral of high risk cases, emergency obstetric care and management of preterm labour and immediate newborn care including neonatal resuscitation.
c. ***Care of healthy newborn,*** by home visits, exclusive breast feeding, clean postnatal practices and immunization.
d. ***Care of sick and small newborn,*** by Kangaroo mother care, Feeding support, IMNCI based interventions and facilities of *Newborn stabilization units* (NBSU) at block level, *Special newborn care unit* (SNCU) at district levels and *Neonatal intensive care units* (NICU) at regional level.
e. ***Care beyond newborn survival*** by screening for birth defects and follow-up of high-risk babies for developmental delay.

Progress: INAP envisages use of SDG targets, e.g. NMR and SBR to review the project every 5 years, apart from other dashboard indicators of global *Every newborn action plan* (ENAP), e.g.: (a) minimum 4 antenatal care visits, (b) skilled birth attendant at delivery, (c) postnatal care within 2 days to mother and baby ad, (d) establishment of SNCUs.

28.3.7 JANANI SHISHU SURAKSHA KARYAKARAM (JSSK)

Considering the difficulties faced by the pregnant women and parents of sick newborn apart from high out of pocket expenses in health care facilities, Janani Shishu Suraksha Karyakaram (JSSK) has been launched since

June, 2011 to motivate pregnant women who still choose to deliver at homes to opt for institutional deliveries

Aims: It aims to provide completely free and cashless services to pregnant women including normal deliveries and cesarean operations and sick newborn up to 30 days after birth (now up to 1 years) in government health institutions of both rural and urban areas.

Implementation: JSSK is implemented by all states and union territories with following benefits:

- **Free Entitlements for pregnant women include:** (a) free and cashless delivery, (b) free C-section, (c) free drugs and consumables, (d) free diagnostics. (e) free diet during stay in the health institutions, (f) free provision of blood, (g) free transport from home to health institutions, between facilities in case of referral and from institutions to home.
- **Free Entitlements for newborns and infants up to 1 year include:** (a) free treatment, (b) free drugs and consumables, (c) free diagnostics, (d) free provision of blood, (e) free transport from home to health institutions, between facilities in case of referral and from institutions to home.

28.3.8 HOME-BASED NEWBORN CARE

Home-based Newborn care (HBNC) is launched under NRHM since 2011 and revised in 2014 to incentivize Accredited Social Health Activist (ASHA) for providing Home-based Newborn Care.

They will visit all newborns according to specified schedule up to 42 days of life to ensure—(a) recording the weight on Mother-child protection card, (b) BCG and first-dose DPT and OPV vaccination, (c) registration of the birth and (d) safety of mother and child till 42 days.

In return, ASHA workers are paid ₹ 250 for total 6 visits for home deliveries and 7 visits for institutional deliveries.

Further, all newborn discharged from SNCUs or Preterms/LBW are followed up by them on day 0 (discharge), 3, 7, 14, 21 and 42 days and then every 3rd month till one year of life, linked with an incentive of ₹ 50 per visit per quarter from 3rd month onwards.

28.3.9 RASHTRIYA KISHOR SWASTHYA KARYAKRAM (RKSK)

Adolescents, generally considered as healthy, are actually at higher risk for many nutritional, life-style, sexual and mental health as well as violence and injuries.

Rashtriya Kishor Swasthya Karyakram (RKSK) was launched on 7th January, 2014 to enable all adolescents to realize their full potential by making informed and responsible decisions related to their health and well-being and by accessing the services and support they need to do so.

Key strength of this program is its *health promotion approach*—a paradigm shift from the existing clinic-based services to promotion and prevention and reaching adolescents in their own environment.

Objectives of this program include: (a) improve Nutrition, (b) improve sexual and reproductive health, (c) enhance mental health, (d) prevent injuries and violence, and (e) prevent substance misuse, among *adolescents.*

Components of this program include:

- Community based out-reach programs to promote adolescent health and nutrition,
- Weekly iron-folic acid supplementation to adolescent boys and girls (100 mg elemental iron with 500 µg folic acid),
- Establishment and strengthening of Adolescent Friendly Health Clinics (AFHC), and
- Promotion of menstrual hygiene scheme to encourage and ensure availability of sanitary napkins.

Adolescent friendly health clinics (AFHC), have been established under RKSK to provide targetted preventive, promotive and curative services to this population, on dedicated days/times to improve availability, accessibility and utilization through trained service providers including health staff and counsellors at existing health centers, out-reach centers, e.g. schools/colleges or through telemedicine or social media.

Now, many governmental, private and voluntary health agencies run dedicated AFHCs, sometimes with different names, e.g. Jagruti, Jigyasa. Maitri, sneha, etc.

AFHCs aims to provide whole gamut of clinical and counselling services on diverse adolescent health issues including: (a) sexual and reproductive health, (b) nutrition, (c) substance abuse, (d) injuries and violence, (e) non-communicable diseases, and (f) mental health (also see Ch 13.5).

28.3.10 NATIONAL VECTOR BORNE DISEASE CONTROL PROGRAMME (NVBDCP)

National Vector Borne Disease Control Programme (NVBDCP) is an umbrella program that aims to prevent and control six common vector-borne diseases-*Malaria, filariasis, kala-azar, dengue, Japanese encephalitis and chikungunya.* Directorate of NVBDCP is the nodal agency for planning and policy making, to be implemented by state agencies.

Under NVBDCP, three major strategies are:

a. Disease management, including early case detection, treatment or referral and epidemic-control;
b. Integrated vector management for transmission risk reduction, including residual sprays and personal protection measures;
c. Supporting interventions including information and communication.

Individual components of this program have been discussed with respective diseases.

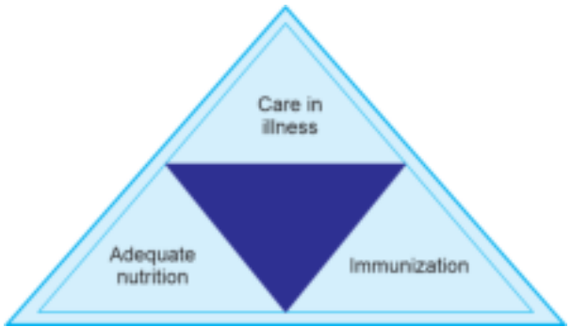

Fig. 28.1: **Under-five clinics: Emblem.**

28.3.11 UNDER-FIVES' CLINICS

Under-fives' clinic is a low-cost strategy to provide promotive, preventive, curative and referral health services for preschool children, within the available resources. Structurally, these clinics may be considered as a modification of '*well-baby clinics*', which mainly provided preventive services.

Objectives: Preschool children account for ~7-8% of total population and ~10% total deaths. Under-fives' clinics target this population with following objectives, which are also enshrined in its emblem **(Fig. 28.1)**:

- ***Care in illness***, e.g. early diagnosis and treatment or referral, of illnesses including growth/developmental abnormalities.
- ***Preventive care***, e.g. immunization, nutritional surveillance and supplementation, periodic health checkups and health education
- ***Growth monitoring*** and recording on a growth chart for ready reference, every month during 1st year, alternate month during 2nd year and then quarterly till 5 years of age.
- ***Family planning services***, denoted as the red central triangle in the emblem, are integrated component of under-fives clinic services.

Organization: These services are mainly provided by ANMs and MPWs, with assistance from non-professionals, e.g. local volunteers and Balwadi workers, after basic training to economize as well as popularize the services. Currently, many of these services have been incorporated with other health care projects, e.g. ICDS.

28.3.12 SCHOOL HEALTH SERVICE

School health service (SHS) is an important component of community health service, aimed to provide comprehensive and integrated health services for school-going children within the available resources. Although existing even before independence, SHS have been strengthened and streamlined after recommendations by a special school health committee 1961, Govt. of India.

Objectives: School-children contribute to ~1/4th of total Indian population, which is highly susceptible to environmental influences as well as easily approachable and amenable to inculcate good health practices. SHS targets this specific population with following objectives:

- Promotion of positive health,
- Prevention of diseases and ill-health,
- Early diagnosis, treatment, referral and follow-up,
- Generation of health consciousness,
- Provision of healthy school environment.

Organization: SHS are provided by special '*school health clinics*', conducted by local PHCs or municipal health agencies on fixed days and time, in coordination with schools' staff within its jurisdiction. A whole-time medical officer is appointed to cover ~5000–6000 children, with additional help from specialists and paramedical workers. Local school health committees are expected to supervise functioning of these services, while National School Health Council acts as an advisory and coordinating body.

Components: Following services are provided under school health services:

- *Health appraisal*:
  - Periodic medical checkups on admission and then, at least every four years.
  - Periodic health check of school personnel, who also form the school environment
- Selective evaluation of any child, suspected as sick by teachers.
- *Remedial measures* including specialist referrals and follow-up.
- *Prevention of communicable diseases*, e.g. immunization.
- *Healthful school environment*, to fulfil minimum standards of spacing, cleanliness, sanitation and water supply.
- *Nutritional services* including mid-day meals and specific supplements, e.g. iron and Vit. A.
- *First aid and emergency care*, via training of teachers to ensure minimum first-aid supply.
- *Mental health* promotion by providing stress-free environment and assistance of school counselors.
- *Dental health* – periodic evaluation and care
- *Eye/ENT health* – periodic evaluation and care.
- *Health education*, with special emphasis on personal and environmental hygiene and family adjustments.
- *Education of handicapped children* to maximize their potential.
- Proper maintenance and use of *health records*.

28.4 SOCIALLY AT-RISK CHILDREN

This chapter deals with some common social problems in some children that render them at a higher risk than their counterparts for physical, mental or social ill health and prevent achievement of full potential. Although

prevalent world over, these problems are common in developing countries, e.g. India, due to social, economic and cultural environment of society.

28.4.1 CHILD ABUSE AND NEGLECT (CHILD MALTREATMENT)

Child abuse and neglect (CAN), also termed as Child Maltreatment by WHO, refers to "*physical, emotional and/or sexual exploitation/abuse, by intention or by negligence, of the children below 18 years of age, by person/s including parents, caretakers, employers or others*".

Clinical spectrum of child abuse includes:

- *Physical abuse* including child labor.
- *Emotional abuse*, e.g. terrorizing or rejection, etc.
- *Sexual abuse* with/without rape, incest, etc.
- *Social abuse*, e.g. sex/caste discrimination, etc.

Prevalence of CAN is difficult to assess, since some amount of child abuse is often considered as a norm for child-rearing in many societies and never reported. As per Government of India data 2007, half to two-third of children aged 5–12 years have been abused physically, sexually or emotionally, more common in girls or children with disabilities.

Consequences: CAN affects the life of a child, not only in terms of immediate physical injuries and sometimes, mortality, but also with long-term physical disabilities, behavioral problems and mental health. Antisocial behavior, additions and delinquency is relatively very common in persons exposed to CAN in childhood.

Determinants: Genesis of CAN is very complex with medical as well as social dimensions. Important high-risk factors for CAN in Indian children are given in **Table 28.10**.

TABLE 28.10: Determinants for CAN

- ***Socio-cultural factors***
  Punitive child-rearing practices
  Gender discrimination
  Family structure: large size, nuclear family
  Parental expectations
- ***Economic factors***
  Poverty
  Unemployment
- ***Parent-related factors***
  Own childhood experiences
  Chronic physical/psychiatric problems
  Drug/alcohol abuse
  Marital disharmony, e.g. single parent
- ***Child-related factors***
  Unwanted sex (Girl child)
  Physical/mental handicaps
  Behavioral problems
  Poor school performance

Diagnosis: Nearly 1/3rd of the cases with child abuse present within first 6 months of life and another 1/3rd during 6 months-3 years of age. Important clinical indicators of child abuse are:

- *Discordant history*
  - Direct complaint by child, relatives or neighbors
  - Discrepant history from two parents.
  - Emphatic parental denial to suspected etiology.
  - Delayed seeking of medical help
- *Mysterious clinical signs*
  - Unexplained superficial injuries, e.g. burns, bruises.
  - Unexplained deep injuries, e.g. head injury, (*Shaken-baby syndrome*) or skeletal injuries/ dislocations
  - Sudden deafness or eye injury, (e.g. subconjunctival bleed)
  - Genital injuries
  - Unexplained failure to thrive
- *Psychological or behavioral changes in child*
  - Timid/revengeful personality
  - Post-traumatic stress disorder (PTSD)
  - Signs of emotional deprivation: poor eye contact
  - Learning disabilities or delinquent behavior
- *Unexplained negative results on investigations*
- *Quick relief during hospitalization or separation from suspected perpetrator, e.g. parents/relatives.*

Management of CAN is a team-effort involving medical personals, social workers, law authorities and NGOs. Pediatrician may play an important role in management of these cases by:

a. Early recognition of possible CAN,
b. Identification of precipitating factors,
c. Reporting to authorities with necessary assistance,
d. Treatment of physical injuries,
e. Emotional support and asking for psychiatrist's assistance, if necessary,
f. Isolation of child from harmful environment, e.g. hospitalization,
g. Care during institutionalization at orphanages, foster homes, etc. and
h. Assistance in rehabilitation efforts.

Prevention of CAN involves: (a) *Attitudinal change* in child-rearing practices, (b) *Remedial measures* to avoid family stress, e.g. poverty, unemployment, alcoholism, marital disharmony, (c) *Avoidance* of unwanted pregnancies, (d) *Parental counseling* services, (e) *Legal remedies* and supervision.

Protection of children from sexual offenses act (POCSO), 2012, amended in 2019, provide a robust legal framework for the protection of children from offences of sexual assault, sexual harassment and pornography, while safeguarding the interest of the child at every stage of the judicial process.

Following offences are included under this act: (a) penetrative sexual assault, (b) touching a child with sexual intent, or making the child touch them or someone else, (c) sexual harassment with remark, gesture, flashing, etc. (d) child pornography, and (e) aggravated penetrative or non-penetrative sexual assault. The act is gender-neutral for both children and for the accused. It provides for minimum punishment for penetrative assault for 10 years (20 years if the victim was <16 years), with a maximum punishment of life imprisonment/death penalty.

Other important constitutional provisions against CAN include section 75 (against cruelty), 76 (abetment of suicide), 317 (abandonment of child < 12 years).

28.4.2 CHILD LABOUR

Child labour is defined as *'Involvement of children (<14 years) in gainful or non-gainful employment, under conditions detrimental/potentially detrimental to their health or physical, mental or emotional development, depriving them their fundamental rights and meaningful education/training opportunities'.*

Magnitude: India fosters the largest number of child labourers in the world, involving ~20 million children in 5–15 years age group. According to an estimate, 15% of Indian children qualify the definition of child labourer, of whom ~ 1/3rd are engaged in full-time economic activity. Others usually work as part-time or casual labourers.

Types: Child labor may be broadly divided into five groups: (a) domestic workers, (b) agriculture labourers, (c) industrial laborers specially in unorganized sector as unskilled workers or apprentices, (d) commercial establishment laborers, e.g. in restaurants, (e) self-employed workers, e.g. rag-picking, shoe-shining and (f) bagging. *Bonded labor* is the worst kind of child labor practice in India, specially in agriculture and domestic sector.

Determinants: Child labor is a consequence of many inter-related social evils, the most important being poverty and illiteracy **(Table 28.11)**.

Consequences: Involvement in labor from a very young age not only prevents the achievement of full growth/developmental potential but also has dire consequences on physical, emotional and social well-being of the child.

TABLE 28.11: Determinants of child labor in India

- ***Economic factors:*** Poverty, unemployment
- ***Social factors:*** Illiteracy, Urban migration
- ***Family factors:*** Large family size, child-parent conflicts
- ***Behavioral factors:*** Truancy, Identity crisis
- ***Bonded labor***, specially in rural areas

Some important consequences of child-labour are as follows:

- *Physical:* Malnutrition, communicable diseases, etc.
- *Occupational:* Accidents, poisonings, abuse, etc.
- *Emotional:* Juvenile delinquency, drug abuse
- *Social* discrimination/deprivation of fundamental rights
- *Educational* lack of opportunities

Prevention: According to International labor organization convention 1973, minimum work-age for most sectors has been established as 15 years, though light work is permitted from 13 years onwards, provided that it does not interfere with child's health, morals, safety and educational objectives.

Child Labor (Prohibition and Regulation) Act, 1986 in India prohibits employment of children in most specified and unspecified occupations, except the family-based work and recognized school-based activities. However, these statutory provisions are difficult to implement, unless root causes, e.g. poverty, adult unemployment and illiteracy are eliminated. Currently, it is more prudent to regulate the working conditions of these children in permitted sectors and protect them from health hazards, exploitation and abuse.

Indian Constitution protects a child from y hazardous employment till 14 years (Article 21A) and guarantees the right to free and compulsory elementary education from 6-14 years [article 24(a)].

28.4.3 STREET CHILDREN

Street children are another high-risk pediatric population, estimated to account for ~ 5–10% of under-14 population in India. Over 70% of them are above 6 years and males.

Ecologically, three major ecological factors for rising population of street children include: (a) poverty, (b) urbanization, and (c) family dys-adaptation.

Issues: Important issues related to street children are: (a) deprived health care and education facilities, (b) lack of sanitary living conditions, (c) safety considerations, e.g. child abuse and exploitation, and (d) high prevalence of drug abuse.

Preventive aspects: Important steps being taken up for improvement of living conditions for street children by various governmental organizations and NGOs are: (a) provision of night-shelters, (b) helplines, (c) security identity cards and (d) correctional and vocational guidance centers.

28.4.4 GIRL CHILD

Girls have been traditionally considered as a member of deprived sex in India, due to various social and cultural factors. Despite major strides by Indian woman in recent

years, the sex ratio – a comprehensive indicator of differential mortality and prenatal sex selection practices in the community-continues to decline unfavorably. Current male-female ratio at birth in India is 1000:933, as against the 972 in 1901. Only the Kerala state in India has a favourable sex ratio of 1058 females *vs.* 1000 males.

Issues: Important issues related to girl child are- (a) prenatal sex determination, (b) female feticide/infanticide, (c) poor nutrition and health care in childhood, (d) female illiteracy, (e) child and sexual abuse, (f) child-marriage, (g) marital dowry system, and (h) low employment wages with financial dependence.

Preventive aspects: Important steps in upliftment of girl child include:

a. Creation of social awareness with the help of IEC activities and mass media,
b. High-risk family counseling,
c. Restriction on pre-natal sex determination (PNDT act)
d. Promotion of female literacy,
e. Targeted nutritional/health care activities and programs,
f. Legislative actions, e.g. reservations and changes in labor law, and
g. Creation of equal job opportunities.

Provisions under POCSO Act, discussed earlier, provide special safeguards to girl children against sexual offenses and exploitation.

28.4.5 HANDICAPPED CHILD

A handicapped child may be defined as "*a child with some disability, which interferes with normal growth, development or capacity to learn and consequently, to achieve maximum potential as a human being*". In this context, the term *disability* refers to "any restriction or lack of ability to perform an activity in a manner or within the range, considered normal for a human being", which may be due to: (a) intrinsic impairment, i.e. anatomical, physiological or psychological dysfunction, or (b) external environment, e.g. neglected or destitute children.

In simple terms, genesis of a handicap may be denoted as a sequence of events, i.e. *disease > functional impairment > disability > handicap*. One handicap may give rise to another, denoted as *primary* and *secondary* handicap, e.g. blindness (primary) leading to illiteracy (secondary).

Incidence: Although difficult to quantify, ~ 5–10% of children in India are estimated to have some kind of handicap/s.

Etiology: According to primary disability, handicapped children may be classified into 3 major categories-*physical, mental and social handicaps*. Malnutrition, perinatal brain injury, infections and accidents account for ~3/4th of handicapped state in children **(Table 28.12)**.

TABLE 28.12: Common handicaps in childhood

- **Physical handicaps**
  - *Anatomical:* birth defects, accidents
  - *Neurological:* cerebral palsy, poliomyelitis
  - *Sensory:* deafness, blindness, dumbness
  - *Chronic diseases:* PEM, epilepsy, asthma, etc.
- **Mental handicaps**
  - Mental retardation
  - Learning disabilities
  - Behavioral problems
- **Social handicaps**
  - Emotional deprivation, e.g. orphans
  - Child abuse and neglect
  - Juvenile delinquency

Management of a handicapped child aims to maximize functional ability, provide the capacity to earn livelihood and restore social relationship, personal dignity and confidence. It may be broadly divided into three stages:

a. ***Primary prevention (disability prevention),*** i.e. control of causative disease by measures, e.g. genetic counseling, good perinatal care, immunization, growth/developmental monitoring and nutritional support.
b. ***Secondary prevention (disability limitation),*** i.e. to prevent progression of disease into a disability by measures, e.g. early diagnosis/treatment of causative disease and identification/modification of adverse environmental factors.
c. ***Rehabilitation*** by physiotherapy, occupational therapy, vocational training and assistance.

However, community participation and family support are key-factors in management of handicapped children.

Rights of Persons with Disabilities Act, 2016 covers 21 disabilities including *Physical* (locomotor, vision, hearing), *Intellectual* (Learning disorders and Autism), *Mental* illness and disabilities due to chronic diseases, e.g. parkinsonism, thalassemia and haemophilia, apart from multiple disabilities. Persons with "benchmark disabilities" are defined as those certified to have at least 40 per cent of the disabilities specified above.

The act entitles them for benefits under various government schemes including reservations in education and jobs, as well as special legal protection against harassment and crime.

28.4.6 JUVENILE DELINQUENCY

Juvenile delinquency (JD), under the children act 1960, is defined as *"an offense committed by a boy <16 years or girl <18 years"*, which includes not only a crime but also any deviation from normal social behavior, e.g. habitual disobedience, truancy and immoral acts.

TABLE 28.13: Risk-factors for juvenile delinquency

- **Biological**
  - Chromosomal excess, e.g. Klinefelter syndrome
  - Physical/mental handicaps
  - ? Hormonal disturbances, sp. in adolescence
- **Social**
  - *Family profile:* Single parents, alcoholism
  - *Child-rearing practices:* Overindulgence/discipline
  - Rapid urbanization and industrialization
- **Economic:** Poverty and unemployment
- **Environmental**
  - Adverse impact of audio-video media.
  - Drug-abuse
  - Adverse peer pressures

Incidence: Although correct estimates are not available, incidence of JD seems to be rising in Indian children due to rapid urbanization, industrialization and cultural changes. JD is more common during late adolescence (>15 years) and in males (4-5:1).

Causes: JD is a complex interplay of many social and environmental factors, though some children seem to be more prone for antisocial behavior and JD due to their biological characteristics **(Table 28.13)**.

Preventive measures: Early detection and rectification of social and family maladjustment as well as control of adverse environmental influences is the key for prevention of JD and involves:

a. Family counseling regarding correct child-rearing practices and child-parent relationship,
b. Healthy child-teacher relationship in schools,
c. Outlet avenues for suppressed anger, e.g. helplines or child-guidance facilities,
d. Provision for appropriate recreation facilities, and
e. Social-welfare schemes including those to control or rehabilitate drug-abuse.

Juvenile Justice Act 2015 (under amendment 2018) aims to protect and care the children in conflict with law, by catering to their needs and adopt a child-friendly approach to reform and rehabilitate them with social reintegration.

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CHAPTER

29

Integrated Management of Neonatal and Childhood Illnesses

Mukesh Agrawal

Integrated management of neonatal and childhood illnesses (IMNCI) is a novel *healthcare strategy*, developed by WHO in consultation with UNICEF and other international agencies in mid-1990s, to facilitate early diagnosis, appropriate case management and timely referral of sick children at primary health care level, as well as to ensure basic preventive interventions.

Need: Experience and available data shows that:

- Acute respiratory infections, diarrhoea, infections, e.g. measles or malaria, and malnutrition account for ~3/4th cases of morbidity and mortality in under-5 children in developing countries.
- Since clinical features of these diseases often overlap and most of them are interrelated, arriving at a single diagnosis is neither easy nor desirable from the treatment point of view.
- Effective and simple interventions are available to manage most of these conditions, e.g. ORS, etc.

Concept: IMNCI is a *move* away from *'single disease'* diagnosis to a *'holistic or syndromic' approach*, different from conventional approach on following grounds:

- **Holistic:** IMNCI stresses on assessment of child as a whole, rather than for specific diseases.
- **Clinical:** A sick child is assessed on the basis of simple clinical signs for primary problems and their severity, rather than by elaborate laboratory workup.
- **Syndromic:** Considering usual presence of coexisting problems, illness is considered as a syndrome rather than specific diagnosis.
- **Simple therapeutic interventions** based on pre-evaluated protocols are used to manage these children.

Objectives: IMNCI aims to:

- Reduce under-5 morbidity and mortality, specially in developing and resource-limited countries.
- Address overall health of child rather than a single disease, to avoid duplication of efforts and wastage of resources.

Components: Major emphasis under IMNCI is on development of cases management skills of health staff and improvement in community health care practices. Important components of IMNCI are:

- *Development of standard case management guidelines* for detection of common health problems and their severity, based on simple clinical signs and empirical treatment protocols.
- *Adoption of these guidelines* after suitable modifications according to local disease patterns, community health care practices and resources.
- *Training of field health staff* to effectively implement these guidelines in practice and provide them with course material/public education material.
- *Ensuring regular supply* of common drugs and basic equipments at field level.
- *Improvement of quality-care at referral centers.*
- *Maintenance of case-management skills* with periodic trainings, checks and supervision.
- *Follow-up evaluation* for lacunae in approach and implementation (a continuous process).

General process: Important steps in IMNCI case management process for sick children, brought at first level health care facility are as follows **(Fig. 29.1)**.

a. **Assessment** of the child for danger signals, main symptoms, nutrition, immunization and other problems.
b. **Classification** of the illness in order to determine the treatment plan, using a color-coded triage system, i.e. *pink* for referral, *yellow* for treatment at primary health care facility and *green* for home management.
c. **Referral** of the seriously sick children to nearby higher health-center after necessary pre-referral treatment
d. **Treatment** of other cases with less severe illnesses at first-level health care facility or at home, along with counseling of caretaker regarding further treatment, follow-up and preventive interventions.

Considering variations in common health problems and reliability of common disease indicators in different age groups, separate sets of IMNCI case management guidelines have been recommended *for—(a) sick children between 2 months up to 5 years of age, and (b) sick infants below 2 months of age.*

WHO has revised these guidelines in 2014 and Government of India has adopted them since 2021, as discussed in following sections.

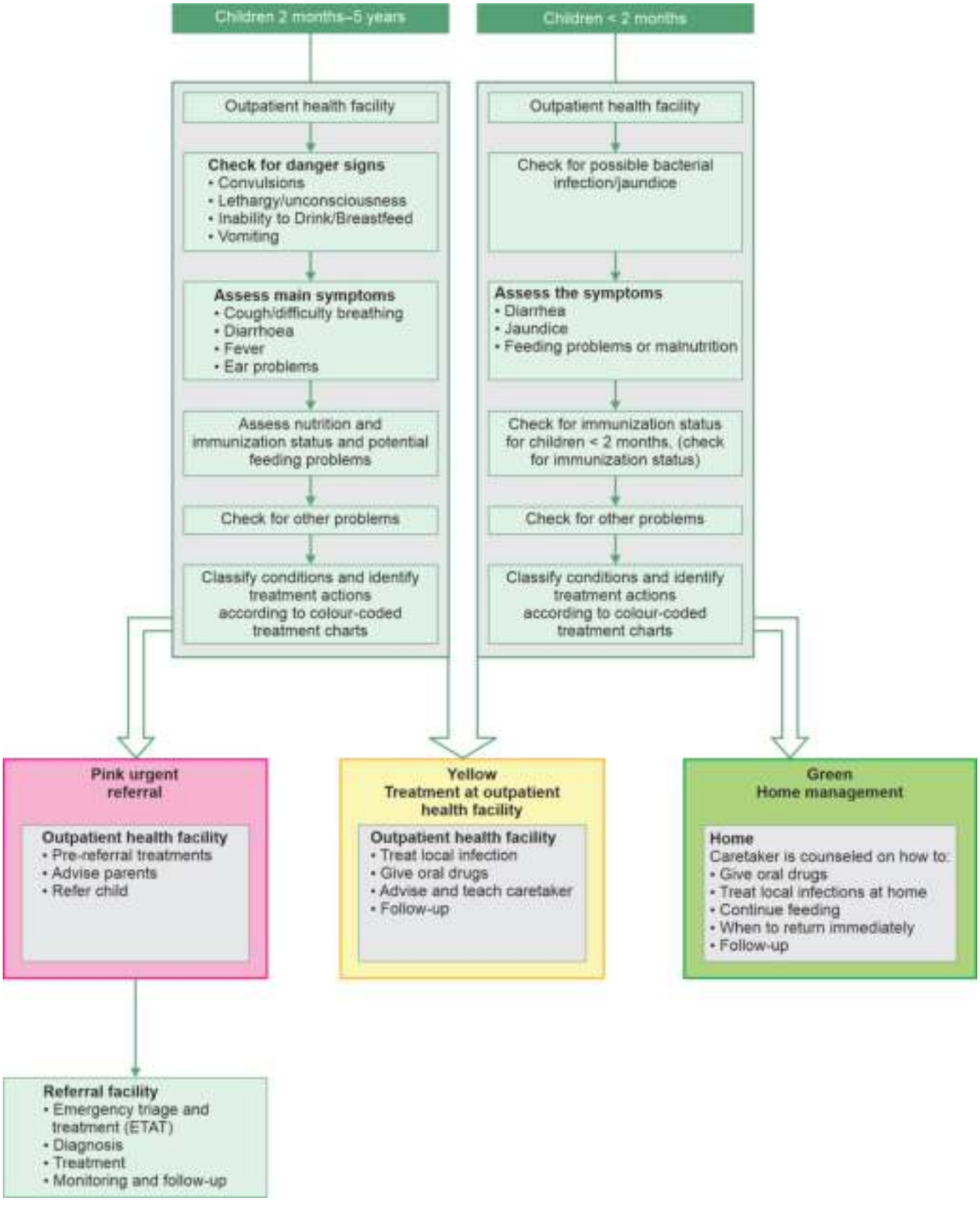

Fig. 29.1: The integrated case management process of IMNCI for child 2 months up to 5 years of age.

29.1 OUTPATIENT MANAGEMENT OF CHILDREN FROM 2 MONTHS UP TO 5 YEARS

Important steps in the management of these cases according to IMNCI guidelines 2021 are as follows:

Step I. Assessment for danger signs: All sick children should be assessed for four important *danger signs*—(a) *convulsions or history of convulsions, (b) lethargy/unconsciousness, (c) inability to drink/breastfeed, and (d) vomiting.*

Presence of any one *or* more of these signals classify these cases as ***"Very severe disease"*** Who need immediate *referral* to hospital after quick evaluation for main symptoms (step II) to decide pre-referral treatment, if required. Baby should be kept warm, treated for low blood sugar if required and must be give rectal diazepam (0.5 mg/kg), if convulsing. Diazepam may be repeated after 10 minutes if convulsions continue.

Step II. Assessment for major symptoms: All sick children, should then be assessed for following *four major symptoms*—(a) cough/difficult feeding, (b) diarrhea, (c) fever, and (d) ear problems.

a. **Children with cough or difficult breathing** must be assessed for—*(a) respiratory rate, (b) chest indrawing, (c) stridor, (d) wheezing, and (e) SpO_2.*

If wheezing with fast breathing/chest indrawing, Give three doses of rapid-acting bronchodilator, i.e Nebulized salbutamol or 2-4 puffs of salbutamol inhaler at 20 minutes interval and reassess again.

Accordingly, they are classified in three categories for severity and treatment purpose as follows—(a) *severe pneumonia* or very severe disease, (b) *pneumonia*, and (c) *no pneumonia*: (cough or cold) **(Table 29.1)**.

b. **Children with diarrhea** must be assessed for: *(a) duration of diarrhea (</>14 day), (b) presence of dehydration, and (c) presence of blood in stools.* Dehydration is assessed on the basis of four signs—*(a) general condition*, e.g. lethargic/unconscious or restless/irritable, *(b) sunken eyes, (c) ability to drink water, and (d) skin turgor or elasticity*, on pinching.

Accordingly, they are classified in six categories for severity and treatment purpose, as follows: (a) severe dehydration, (b) some dehydration, (c) no dehydration, (d) severe persistent diarrhea, (e) persistent diarrhea, and (f) dysentery **(Table 29.2)**.

c. **Children with fever** are first assessed for the risk of *falciparum malaria* (endemicity) and *dengue* (season), followed by evaluation for: *(a) duration of fever, (b) stiff neck, (c) septic focus, (d) signs of active measles, e.g. rash, cough, runny nose or red eyes, (e) H/o measles in past 3 months with presence of mouth ulcers or pus discharge from eyes.*

Dengue must be suspected in children with fever 2–7 days during dengue season, who should also be assessed for warning signs: (a) cold extremities with thread pulse, (b) severe abdominal pain, (c) bleeding, and (d) positive tourniquet test.

A Rapid diagnostic test (RDT) for malaria is advised to all fever cases in endemic area or in a fever case with no other cause in non-endemic area.

Accordingly, fever cases are classified in eight categories for severity and treatment purpose as follows: (a) very severe febrile illness, (b) malaria/suspected malaria, (c) fever, malaria unlikely, (d) severe dengue/dengue with warning signs, (e) dengue fever, (f) severe complicated measles, (e) measles with eye or mouth complications, and (f) measles **(Table 29.3)**.

d. **Children with ear complaints** are assessed for—*(a) ear pain, (b) pus discharge from ears and its duration (c) tenderness behind the ears.*

Accordingly, these cases are classified in four categories for severity and treatment purpose as follows: (a) mastoiditis, (b) acute ear infection, (c) chronic ear infection and (d) no ear infection **(Table 29.4)**.

Step III. General assessment: After assessment for general danger signals and major symptoms, children must be assessed for—*(a) nutrition, (b) anemia, and (c) immunization status,* and *(d) feeding problems.*

a. **Nutrition** is assessed by—*(a) weight for length/height (WFL), (b) presence of bilateral feet edema, (c) mid upper-arm circumference (MUAC) above 6 months, and (d) any medical complication, e.g. general danger sign, any severe classification, pneumonia, diarrhea with dehydration and poor appetite.*

TABLE 29.1: IMNCI classification for cough/difficult breathing (2 months – 5 years)

Severe pneumonia or very severe disease
Signs: (a) Any general danger sign, (b) Stridor, (c) SpO_2 <90%. **Treatment:** • Give first dose of IM antibiotics • Refer urgently, ensure warmth during transfer • Provide oxygen on the way to hospital
Pneumonia
Signs: (a) Fast breathing, (b) Chest indrawing **Treatment:** • Give oral amoxicillin for 5 days • Inhaled/oral salbutamol for 5 days, if wheezing • Safe home remedies[1] in children > 6 months • Follow-up after 2 days or SOS
No Pneumonia
Signs: No sign of pneumonia/severe pneumonia **Treatment:** • Inhaled/ oral salbutamol for 5 days, if wheezing • Safe home remedies[1] in children > 6 months • Follow-up after 5 days or SOS • Referral, if cough persists for > 30 days

[1]Safe home remedies to sooth the throat, e.g. honey, tulsi, ginger, etc.

TABLE 29.2: IMNCI classification for diarrhea (2 months – 5 years)

Severe Dehydration

Signs: (any two)
(a) Lethargic/unconscious, (b) Sunken eyes, (c) Inability to drink (d) Very low skin turgor
Treatment:
- Give IV fluids as WHO-Plan C
- Refer urgently (if has another severe classification)
- Advise ORS and breastfeeding during transfer
- PO antibiotics, if there is cholera outbreak (in children > 2 year)

Some Dehydration

Signs: (any two)
(a) Restless/Irritable, (b) Sunken eyes, (c) Thirsty, drinks eagerly, (d) Low skin turgo
Treatment:
- Give ORS/oral fluid as WHO-Plan B
- Give Zinc and continue foods
- Refer urgently (if has another severe classification)
- Advise ORS and breastfeeding during transfer
- Follow-up after 5 days or SOS

No Dehydration

Signs: Not enough signs for some/severe dehydration
Treatment:
- Give ORS/oral fluids as WHO-Plan A
- Give Zinc and continue foods
- Follow-up after 5 days or SOS

Severe persistent diarrhea

Signs: Diarrhea >14 days with dehydration
Treatment:
- Refer urgently (if has another severe classification)
- Treat dehydration, before referral (if no other severe classification)

Persistent Diarrhea

Signs: Diarrhea >14 days without dehydration
Treatment:
- Advice on feeding
- Give oral vitamin A (single dose)
- Give oral zinc and multivitamins for 14 days
- Follow-up after 2 days

Dysentery

Signs: Blood in stool
Treatment:
- Give oral Cefixime for 5 days
- Give oral Zinc for 14 days
- Follow-up after 2 days

Accordingly, the child is classified into four nutritional categories for severity and treatment purpose—(a) severe acute malnutrition (SAM) with medical complications, (b) SAM without medical complications, (c) moderate acute malnutrition, and (d) no acute malnutrition **(Table 29.5)**.

b. **Anemia** is assessed according to the *color of child's palm* and comparing it with examiner's palm, though haemoglobin should be tested, if possible.

TABLE 29.3: IMNCI classification for fever (2 months – 5 years)

Very Severe Febrile Illness

Signs: (a) Any general danger sign or (b) Stiff neck
Treatment:
- Give first dose of IM antibiotics
- Give fist dose of artesunate/quinine (if RDT+/Malaria endemic)
- Treat/prevent hypoglycaemia
- Give one dose of paracetamol, if fever >38.5°C
- Refer urgently (or treat if referral not possible)

Malaria/suspected malaria

Signs: RDT + ve /not possible and no other alternative cause
Treatment:
- Give oral antimalarials as per national guidelines
- Give one dose of Paracetamol, if Fever >38.5°C
- Follow-up after 2 days or SOS

Fever, Malaria Unlikely

Signs: Negative RDT, other cause present
Treatment:
- Give one dose of paracetamol, if fever >38.5°C
- Treat possible cause
- Follow-up after 2 days or SOS
- Reassess if fever continues for > 7 days

Severe Dengue Syndrome With Warning Signs

Signs: (any one)
(a) Any general danger Signs, (b) Cold extremities with weak/rapid pulse (c) Severe abdominal pain (d) Bleeding from any site (e) Positive tourniquet test
Treatment:
- Give first dose of IM antibiotics
- Refer urgently
- Plenty of oral fluids/ORS on the way to hospital
- Give one dose of paracetamol, if Fever >38.5°C

Dengue Fever

Signs: No warning signs
Treatment:
- Give one dose of paracetamol, if Fever >38.5°C
- Advice home care
- Follow-up after 2 days or SOS

Severe Complicated Measles

Signs: (Measles now or in last 3 months) and
Any general danger signs, or clouding of cornea, or Deep/extensive mouth ulcers
Treatment:
- Give first dose of IM antibiotics
- Give single oral dose of vitamin A
- Give antibiotic eye ointment if eye signs
- Refer urgently (or treat if referral not possible)

Measles with Eye/Mouth Complications

Signs: (Measles now or in last 3 mo) and
Pus draining from eyes or oral ulcers
Treatment:
- Give single oral dose of Vitamin A
- Give antibiotic eye ointment if eye signs
- Give gentian violet for oral ulcers
- Follow-up after 2 days

Measles

Signs: Measles now or in last 3 months
Treatment:
- Give single oral dose of vitamin A

TABLE 29.4: IMNCI classification for child with ear problems (2 months – 5 years)

Mastoiditis

Signs: Tender swelling behind the ear
Treatment:
- Give first dose of IM antibiotics
- Refer urgently
- Give one dose of paracetamol for pain

Acute Ear Infection

Signs: (a) Pus discharge <14 days or (b) Ear pain
Treatment:
- Give Oral amoxicillin for 5 days
- Dry the ear with wicking
- Follow-up after 5 days or SOS

Chronic Ear infection

Signs: Pus discharge from ear for >14 days
Treatment:
- Dry the ear by wicking
- Topical Quinolone ear drops for 2 weeks
- Follow-up after 5 days

No Ear Infection

Signs: No ear pain or discharge
Treatment:
- No additional treatment

TABLE 29.5: IMNCI classification for malnutrition (2 months – 5 years)

Severe Acute Malnutrition with Medical Complications

Signs: (a) WFL <-3 SDS, or (b) MUAC <11.5 cm, or (c) B/L pedal edema and medical complication
Treatment:
- Give first dose of IM antibiotics
- Refer urgently, ensure warmth during transfer
- Treat/preventive hypoglycemia

Severe Acute Malnutrition without Medical Complications

Signs: (a) WFL <-3 SDS, or (b) MUAC <11.5 cm, and No medical complication
Treatment:
- Give oral amoxicillin for 5 days
- Give Single oral dose of vitamin A
- Give multivitamins and zinc for 14 days
- Dietary assessment and counseling
- Follow-up after 7 days or SOS

Moderate Acute Malnutrition

Signs: (a) WFL <-3 to <-2 SDS, or (b) MUAC 11.5 -12.4 cm
Treatment:
- Dietary assessment and counseling
- Follow-up after 7 days or SOS

No Acute Malnutrition

Signs: (a) WFL > -2SDS, (b) MUAC > 12.5 cm, (c) No edema
Treatment:
- Dietary assessment and counseling
- Follow-up after 2 day or SOS

WFL: Weight for length; **MUAC:** Mid-upper arm circumference (not applicable <6 mo age)

TABLE 29.6: IMNCI classification for anemia (6 months – 2 year)

Severe Anemia

Signs: Severe palmer pallor (Hb <7 gm/dl)
Treatment:
- Refer urgently

Some Anemia

Signs: Some palmar pallor (Hb 7–10.9 gm/dl)
Treatment:
- PO Iron-Folic acid for 14 days
- Dietary assessment and counseling
- Follow-up in 14 days or SOS

No Anemia

Signs: No palmar pallor
Treatment:
- Prophylactic iron-folic acid (if >6 month old)

Accordingly, classify the child to three categories for severity and treatment purpose: (a) severe anemia, (b) anemia, (c) no anemia **(Table 29.6)**.

c. **Immunization status** of every sick child must be assessed by history and review of immunization card, along with status of Vitamin A and folic acid supplementation. All missed/due immunizations may be given to sick child, though very sick children, being referred urgently to higher hospitals, should not be immunized as vaccine may be wrongly blamed in the event of child's death.

d. **Feeding problems** must be assessed in all babies <2 years with uncomplicated SAM, MAM and anemia, with special reference to: (a) *breastfeeding* - frequency, night-feeds, etc., (b) *complimentary feeds*, and (c) *feeding during current illness*. Mother should be advised appropriately in cases with feeding problems. She must also be praised for correct practices.

Step IV. Assessment for other problems: Although IMNCI guidelines focus of main symptoms, many other problems, e.g. conjunctivitis, may co-exist in sick children that need to be recorded and managed accordingly.

Step V. Referral to the hospital: Following categories of cases (Pink-color code) needs ***urgent referral:*** (a) severe pneumonia or very severe disease, (b) severe persistent diarrhea, (c) very severe febrile illness, (d) severe dengue/dengue with warning signs, (e) severe complicated measles, (f) mastoiditis, (g) severe acute malnutrition with complications, and (h) severe anemia (in addition to those with General Danger Signals - Step I).

Cases of diarrhea with severe or some dehydration need urgent referral *only*, if some other severe classification is present. Some other categories of cases may also need Non-urgent referral after follow-up.

Referral note to the hospital should include: (a) name and age of patient, (b) date and time of referral, (c) description of child's problem, (d) reasons for referral, (e) treatment given, and (f) any other information.

Pre-referral treatment: All these cases should also receive essential ***pre-referral treatment***, e.g. (a) first dose of antibiotics (Ampicillin and Gentamycin), (b) antimalarial as per national guidelines including artesunate or quinine, if from falciparum prevalent area or having positive RDT, (c) prevention of hypoglycemia by giving breast milk or sugar water, (d) prevention of hypothermia by skin to skin contact, (e) others, e.g. ORS, paracetamol, vitamin A, etc. (*see* related tables). A convulsing child should receive IV or rectal diazepam 0.2 mg/kg before referral.

Step VI. Treatment at the outpatient clinic: IMNCI guidelines provide specific treatment recommendations for cases with less severe classifications (yellow or green code) or those with severe classification *but referral not possible*, which must be administered at the clinic undersupervision or at home after proper counseling to the mother or caretaker (*see* relevant tables).

These interventions also include feeding advice, necessary immunizations and teaching the mother to given oral drugs at home. Mother should also be trained to recognize signs that need urgent follow-up.

Step VII. Follow-up: All cases with less severe classifications (Yellow/Green) must be asked to follow-up immediately if—*(a) unable to accept breast-feeds or drink liquids, (b) become sicker, or (c) develop fever, fast breathing, difficult breathing or blood in stools.* IMNCI guidelines recommends specific follow-up periods in other cases, as specified in tables.

29.2 OUTPATIENT MANAGEMENT OF CHILDREN BELOW 2 MONTHS (SICK YOUNG INFANTS)

Considering special characteristics of very young infants, e.g. non-specificity of clinical presentations, limited value of clinical signs and higher risk of rapid deterioration during an illness, separate guidelines have been recommended under IMNCI for management of children < 2 months (termed as *sick young infants*) as follows:

Step I. Assessment for possible serious bacterial infection: All sick young infants should be assessed for following indicators of possible bacterial infection—*(a) history of feeding difficulty, (b) history of convulsion, (c) fast breathing > 60/min, (d) severe chest indrawing, (e) axillar temperature >37.5°C, (f) movements of the child on his/her own or on stimulation, and (g) umbilical discharge, or (h) presence of skin pustules.*

Accordingly, all babies are classified in following five categories—(a) possible serious bacterial infection, (b) pneumonia, (c) local bacterial infection, (d) infection unlikely **(Table 29.7)**.

Step II. Assessment for jaundice by—*(a) asking the day on onset, and (b) checking the presence of jaundice on skin as well as on palms and soles.*

TABLE 29.7: IMNCI classification for possible serious bacterial infection (Age up to 2 months)

Possible Serious Bacterial Infection or Very Severe Disease
Signs: (Any one) (a) Not able to feed well, *or* (b) Severe chest indrawing, *or* (c) Convulsions, *or* (d) Axillary temperature > 37.5/<35.5°C, *or* (e) No movements or movements only on stimulation **Treatment:** • Give first dose of IM antibiotics • Treat/prevent hypoglycemia • Refer urgently, ensure warmth during transfer
Pneumonia
Sign: Fast breathing (RR >60 after 7th day) **Treatment:** If low weight or has other severe classification • Give first dose of IM antibiotics • Refer urgently, ensure warmth during transfer If not low weight or has no other severe classification • Give oral Amoxicillin for 5 days • Advise home care • Follow-up after 2 days or SOS
Local Bacterial Infection
Signs: (a) Umbilical redness/pus discharge, or (b)Pustules **Treatment:** • Give oral amoxicillin for 5 days • Advise home care • Follow-up after 2 days or SOS
Infection Unlikely
Signs: No signs of bacterial infection/very severe disease **Treatment:** • Advise home care

Accordingly, all babies are classified in following three categories—(a) severe jaundice, (b) jaundice, (c) no jaundice **(Table 29.8)**.

Step III. Assessment for diarrhea: All sick young infants should be assessed for the presence and severity of diarrhea, i.e. increased frequency and/or liquidity of stools from the usual pattern. Note that even normal stools in breast-fed infants are generally more frequent and liquid and should not be construed as diarrhea.

All sick young infants with diarrhea must be assessed for—*(a) dehydration*, and *(b) blood in stools.* Presence of dehydration is assessed by—*(a) general condition*, spontaneous movements, sluggish movements or movements only on stimulation, no movements on stimulation or irritability/restlessness, *(b) sunken eye balls, and (c) loss of skin turgor.*

Accordingly, these cases are classified in three categories—(a) severe dehydration, (b) some dehydration, (c) no dehydration, **(Table 29.9)**. Presence of blood in stools needs referral for evaluation.

TABLE 29.8: IMNCI classification for jaundice in young infant (Age up to 2 months)

Severe Jaundice

Signs:
(a) Jaundice < 24 hr of age, or (b) Yellow palm and soles
Treatment:
- Refer urgently, ensure warmth during transfer
- Treat/prevent hypothermia

Jaundice

Signs:
(a) Jaundice > 24 hrs age, or (b) Palms and soles not yellow
Treatment:
- Advise about home care
- Follow-up if palm/soles become yellow
- Refer if jaundice persists > 14 days

No Jaundice

Signs:
No jaundice
Treatment
- Advice home care

TABLE 29.9: IMNCI classification for diarrhea in young infants (Age up to 2 months)

Severe Dehydration

Signs: (Any two)
(a) Lethargic/unconscious (b) Sunken eyes,
(c) Inability to drink (d) Very low turgor
Treatment:
If any other severe classification
- Give first dose of IM antibiotics
- Refer urgently, ensure warmth during transfer
- Advice to continue ORS and breastfeeding during transfer

If no other severe classification
- Give IV fluids (WHO-Plan C) and then refer to hospital

Some Dehydration

Signs: (Any two)
(a) Restless/Irritable (b) Sunken eyes
(c) Thirsty, drinks eagerly (d) Low skin turgor
Treatment:
If low weight for age or has another severe classification
- Give first dose of IM antibiotics
- Refer urgently, ensure warmth during transfer
- Advice to continue ORS and breastfeeding during

If not low weight for age or no other severe classification
- Give oral fluids (WHO-Plan B)

No Dehydration

Signs: Not enough signs for some/severe dehydration
Treatment:
- Give ORS (WHO-Plan A)
- Continue breastfeeding
- Follow-up after 2 days

TABLE 29.10: IMNCI classification for feeding problems (Age up to 2 months)

Very Low Weight

Signs: (a) Weight <1800 gm < 7 days or (b) Weight < 3 SD from 7-59 days
Treatment:
- Refer urgently, ensure warmth during transfer
- Treat/prevent hypoglycaemia

Feeding Problem or Low weight for age

Signs: (any one)
(a) Poor attachment, (b) Poor sucking, (c) < 8 feeds per day
(d) Fed on other food/drinks, (e) Oral thrush
(f) Low weight for age, (f) Breast and nipple problems
Treatment:
- Advise to avoid other food/drinks
- Increase frequency of breastfeeding
- Advise correct position and attachment during breastfeeding
- Advise local animal milk with cup/spoon, if necessary
- Manage breast/nipple problems
- Treat oral thrush
- Follow-up for feeding problems after 2 days
- Follow-up for low weight after 14 days

No Feeding Problem

Sign: Weight for age >-2SD and no other signs of poor feeding
Treatment:
- Advise the mother about baby care at home
- Praise mother for feeding the infant well
- Follow-up SOS

Step III. Assessment of feeding problem and malnutrition includes: *(a) history* regarding frequency of breast feeding, difficulties in feeding and any top feedings, etc., *(b) examination* during the act of breastfeeding for signs of good attachment, effective sucking, pain to mother while feeding (breast/nipple problems, e.g. sore nipples), *(c) mesurment of body weight* record, and *(d) oral cavity examination* for thrush.

Accordingly, an infant is classified as: (a) very low weight, (b) feeding problem or low weight for age, and (c) no feeding problem **(Table 29.10)**.

Step IV. Assessment of immunization status: All due immunizations may be given to sick young infant, provided s/he is not sick enough to require urgent referral.

Step V. Assessment of other problems: Mentioned by mothers or observed during examination. All young infants with potentially serious problems should be referred to higher center.

Step VI. Referral to the hospital: Following categories of cases (Pink color code) needs ***urgent referral***—(a) possible serious bacterial infection or very severe disease, (b) pneumonia with low weight for age, (c) severe jaundice, and (d) very low weight. Cases of diarrhea with severe or some dehydration need urgent referral only if any other severe classification is present.

Some other categories of cases may also need non-urgent referral after follow-up.

A proper referral note, discussed earlier, should accompany the child.

All these cases should also receive essential ***pre-referral treatment***, e.g. (a) first dose of antibiotics

(IM Ampicillin and Gentamycin, (b) treatment/prevention of hypoglycemia by giving breast milk or sugar water, (c) treatment/prevention of hypothermia by skin to skin contact, i.e. Kangaroo mother care, etc.

Step VII. Treatment at the outpatient clinic: IMNCI guidelines provide specific treatment recommendations for cases with less severe classifications (yellow or green code) or those with severe classification *but referral not possible*, which must be administered at the clinic under supervision or at home after proper counseling of mother or caretaker (*see* relevant tables). These interventions also include teaching the mother about correct feeding practices, temperature care and administration of oral drugs at home. Mother should also be trained to recognise signs that need urgent follow-up.

Step VIII. Follow-up: All cases with less severe classifications (Yellow/Green) must be asked to follow-up immediately *if—(a) unable to accept breast-feeds or drink liquids, (b) become sicker or (c) develop fever, fast breathing, difficult breathing or blood in stools.* IMNCI guidelines recommends specific follow-up periods in other cases, as specified in tables.

Advantages: IMNCI approach has huge potential for success in developing countries like India, as:

a. It addresses nearly all major health problems, responsible for >80% childhood deaths.
b. It is cost-effective and helps in better utilization of available resources for genuine cases.
c. It obviates the need for elaborate laboratory workup in most cases.
d. It promotes curative as well as preventive health care.
e. IMCI approach has shown major impact on health status in other countries, where it has been adopted.

Current status: IMNCI has been accepted as one of the main strategies under NRHM and RCH-II program, to prevent and manage common childhood illnesses. It has been also included as an essential component of training in medical curriculum. However, these guidelines include most, but not all, common childhood conditions, excluding conditions, e.g. trauma and chronic illnesses, e.g. HIV. Wider acceptance of these guidelines by medical fraternity is still not up to the mark. Further, operational aspects of this approach also need collaboration with other health programs and strengthening of referral care services.

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CHAPTER

30

History Taking in Pediatrics

Mukesh Agrawal

Evaluation of a child presenting in the health care involves four key components, often referred with acronym **HELP**, i.e. ***H****istory*, ***E****xamination*, ***L****ogical deduction and* ***P****lan of investigation.* Present chapter outlines broad guidelines regarding history-taking, the first step in evaluation process.

History taking in Pediatrics is an art that can only be perfected by practice. While the broad principles of history-taking in children is same as in adults, two important differences are noteworthy: (a) pediatric history is usually a *third-party history* from the parents, subject to adulteration by their own concerns, beliefs and emotions, (b) history-taking in children cannot be custom-made and must be tailored according to the age with different points of emphasis in different age groups, and (c) it also includes some unique and additional aspects, e.g. perinatal, developmental, dietary and immunization histories.

General considerations: A good history needs a reliable informant, good rapport with child and informant, appropriate questions and questioning techniques, correct interpretation of responses and proper documentation of information. Some important prerequisites for good history are as follows:

- **Environment:** History must be recorded in a quiet and comfortable setting to ease the anxiety of patient with due concerns to the privacy. Adolescent Girls must be interviewed only in presence of a female nurse or relative.
- **Rapport-building:** Development of good rapport with child and parents is essential to get reliable information and useful strategies include: (a) greet and introduce yourself, (b) address the child with name, (c) establish good eye-contact, (d) converse in a empathetic manner, (e) listen attentively without unnecessary interruptions, (f) avoid distractions, e.g. phone calls, and (g) assure them about confidentiality.
- **Informant:** Children are often accompanied by both parents and sometimes with relatives, all eager to provide their own versions of history which may be contradictory. A good history is often influenced by intellect and emotions of informant. Mother is the usually the most reliable and preferred informant. In case of acute event, e.g. seizure or fall, the history must be recorded from the person who actually witnessed the event, if possible. Hearsay history must be avoided. Older children often provide good history and must be offered to tell their concerns, privately if necessary.
- **Questioning** must be in a conversational rather than interrogational manner. Begin with open-ended questions, e.g. "*What is wrong…*" to allow the informant to narrate the history in her/his own words without unnecessary interruptions. Subsequently, identify the points which need clarification and use close-ended questions to get the desired answer, e.g. "*Is it the first time…*". Ask about each complaint separately to ensure accurate response. Let the parents/child choose the language for conversation and use a mutually acceptable interpreter, if necessary. Generally follow the broad sequence of history-taking, as discussed here, to avoid missing any important information. However, move over to the next question if child/parent becomes agitated or upset in response to some question, unless the information is vital to immediate intervention.
- **Interpretation:** Responses from the informant are often influenced by their concerns, intellect and emotions. Listen carefully to the informant's narration of events and answers to close-ended questions. Also observe his/her behavior and non-verbal clues, e.g. hesitancy, avoidance to answer, change in tone or attitude or lack of concern. However, don't argue, ignore or embarrass the informant or laugh on answers.
- **Documentation:** Correct documentation of the history is essential not only for future reference but also for legal purpose. Record the history in pre-structured format as soon as possible, though preferably after the interview is complete to avoid interruptions in narration. Avoid abbreviations as much as possible and use diagrams, etc. to depict pictorial information,

e.g. distribution of rash. Date and time of history-taking must be clearly stated.

- ***Closure:*** At the end of interview, ask for any other concern that the parents have and praise them for nice history or action they have taken before coming to you. Answer their questions and concerns, as truthfully as possible.

Components of history taking: While the emphasis may vary in individual case according to the age and expected clinical problems, a general protocol of history taking in children should include following components - **(Table 30.1)**:

1. Demographic data is essential not only for the purpose of identity but to assist in differential diagnosis and follow-up.

- ***Name*** must be recorded fully and correctly to establish the identity, specially to avoid problems in matters related to medico-legal and insurance issues. Addressing the child with name also helps to develop a rapport with him.
- ***Age*** must be recorded in *completed* time-units appropriate for age, i.e. in *hours* during first 3 days of life, in *days* during later neonatal period, in *months* till 1–2 years of age and then in *years.* Apart from a part of identity, age also assists in the differential diagnosis due to age-wise differences in prevalence of many diseases, e.g. genetic disorders.
- ***Gender*** must be recorded carefully, specially in cases of newborns and ambiguous genitalia. In later case, the child may be labelled as Bisexual, rather than assigned a gender preferred by parents. Apart from a part of identity, gender also assists in the differential diagnosis due to sex-wise differences in prevalence of many diseases, e.g. X-linked recessive disorders.
- ***Religion and caste*** information, though a sensitive issue sometimes, helps in considering the possibilities of diseases common in certain ethnic groups, e.g. sickle cell anemia in Tribals or Thalassemia in Sindhis.

TABLE 30.1: Components of pediatric history

1.	Demographic data
2.	Presenting complaints
3.	History of present illness
4.	System-review
5.	Past history
6.	Family history
7.	Perinatal history
8.	Dietary history
9.	Immunization history
10.	Developmental history
11.	Personal history
12.	Socio-economic history
13.	Environmental history

- ***Address*** must be recorded as complete postal address with contact phone number, to assist in follow-up. Residential information also helps in differential diagnosis as some diseases have well defined geographical distribution, e.g. *Kala-azar* in Bihar.

2. Presenting complaints, also termed as *chief complaints*, form the *seed* of clinical history, enlisting the main reasons for seeking medical care. Important aspects of writing these complaints are as follows:

- All presenting complaints must be recorded chronologically in *a list format*, including brief *telegraphic* description along with duration. A short adjective to convey the character of complaint, e.g. acute, progressive, severe, etc. may be added **(Table 30.2)**.
- Each complaint must be recorded in the exact words of informant and not in medical terms, e.g. write *bluish discoloration rather than cyanosis*. However, unnecessary description may be truncated for the sake of brevity.
- All major complaints which developed after the onset of illness must be included, even if some of them have been resolved by now, either spontaneously or after treatment. In chronic illnesses, e.g. nephritic syndrome, chief complaints may be structured to include whole duration of illness, rather than limiting to presenting complaints. In some cases, e.g. cerebral palsy, this section may begin since birth.
- Include a known and documented diagnosis before listing the complaints to assist in analytic process. For example, begin with *"A known case of Nephrotic syndrome, presents with…."* However, any diagnosis, told by parents but not substantiated by documents must be considered with caution, to avoid diagnostic bias.

3. History of present illness, also termed as *ODP (Onset-duration - progress) history*, is an expanded description of presenting complaints, along with record of trivial complaints ignored in previous section and important negative histories to exclude associated problems. Important aspects of writing history of present illness are as follows:

- It should be written in a *concise but flowing narrative or story* format, elaborating each complaint separately with emphasis on characteristics and course of the illness **(Table 30.3)**.
- It should begin with a statement demarcating the onset of illness, e.g. *"baby was apparently alright till .... days back"*
- Details of any investigation or treatment received during the course of illness must be included, after checking with records. However, any information

TABLE 30.2: Presenting complaints (example)

• High-grade intermittent fever ...	14 days
• Persistent dry cough ...	10 days
• Progressive breathlessness ...	7 days
• Generalized convulsion once ...	2 days back

TABLE 30.3: Exploratory key points in history of present illness

Key points	*Preferred descriptive terms*
• Onset	Sudden or gradual
• Duration	In days/months or from ...years of age
• Character	Intermittent, persistent, dull. Forceful, etc.
• Severity	Mild, moderate, severe, incapacitating
• Course	Progressive, static, improving, episodic
• Variations	Diurnal or postural
• Influencing factors	Aggravating or relieving factors, e.g. meals
• Interventions	Medications, investigations, hospitalization

prior to the onset of first complaint must be recorded in the past history.

4. System review is the *fishing expedition* to search for missed complaints, considered too trivial by the parents and omitted unintentionally. A quick system review helps to identify involvement of other organs/systems, either incidentally or as complication of the presenting illness. Important components of system review include:

- It should be *relevant* to broad differential diagnosis, based on the history of present illness.
- It should be *quick* but *comprehensive*, covering common complaints related to organ/systems other than those recorded earlier **(Table 30.4)**. Any new positive and significant history, discovered during system review, must be recorded in detail.
- *Negative histories* must be recorded, only if relevant.

5. Past history must include details of all significant health events prior to the onset of present illness with special emphasis on: (a) *major illnesses*, (b) *hospitalization, medications or transfusions*, (c) *injuries or surgical interventions, and* (d) *allergic or other adverse events*. Important points in the past history are:

- Any event that occurred in the past but continues to affect the health significantly, e.g. post-stroke hemiplegia must be included in the present than in past history.
- Attempt should be made to strengthen past history with review of previous health records

6. Family history aims to identify genetic as well as shared environmental risk factors, which can influence child health. Getting a reliable family history may be challenging as parents often tend to hide embarrassing facts and must be reassured about the confidentiality. Important aspects of family history are as follows:

- Enquire about similar illness in other family members, indicative of common genetics or shared environment, e.g. infection or toxin exposure.
- Prepare a family tree or Pedigree chart **(Fig. 11.7)** including three generations–siblings, parents and grandparents, to assess the possibility of genetic basis and mode of inheritance.
- Search for similar illness in unrelated household members, e.g. servants, etc., which may suggest environment basis of disease, e.g. tuberculosis.

  Contact may be further specified as household contact or close-contact, who is not a household member but shares an enclosed space, e.g. workplace for extended periods during the day in preceding 3 months.
- Assess the psychosocial environment of the family with special reference to marital conflicts, psychiatric illnesses, substance abuse and child rearing practices.

TABLE 30.4: System review

System/Organ	*Common symptoms (not limited to)*
General	Appetite, sleep, activity, play, school performance
Head	Head injury, headache
Eyes	External problems e.g. redness or discharge, vision problems, injury
Ears	Hearing problems, pain, discharge
Nose	Runny nose, stuffiness, epistaxis
Oral cavity	Feeding difficulty, painful ulcers, dental pain, sore-throat
Neck	Pain, swelling, restricted movements
Skin	Rash, edema, itching, injuries, bruises
Gastrointestinal	Vomiting, diarrhea, abdominal pain, constipation, jaundice
Respiratory	Breathlessness, cough, wheeze, stridor, chest pain
Cardiovascular	Palpitation, cyanosis, edema, fainting, recurrent chest infections
Neurologic	Altered behavior, seizures, weakness, abnormal movements, problems in gait or balancing
Genitourinary	Dysuria, oliguria, frequency, nocturnal enuresis, hematuria, urinary stream, urethral/vaginal discharge, menstruation
Musculoskeletal	Injuries, deformities, joint or muscle pain/swelling, weakness, restricted movements
Hematologic	Pallor, mucocutaneous bleeds, transfusions
Psychiatric	Temperament, behavioral problems, drug-abuse

7. Perinatal history is more relevant in infants and young children with congenital malformations or unexplained chronic diseases and includes:

- ***Antenatal history*** related to: (a) maternal age, nutritional status and general health problems, (b) consanguinity (Ch 11.3), (c) obstetric history, (d) antenatal care and investigations; (e) potential exposure to infections, drugs, toxins or radiation, and (e) significant prenatal complications, e.g. eclampsia, gestational diabetes, etc.
- ***Birth history*** must include: (a) place of delivery, (b) mode of delivery, (c) obstetric complications, e.g. meconium staining, (d) need for neonatal resuscitation, and (e) gestational age and birth weight.
- ***Immediate postnatal history*** must include information about: (a) early infant feeding, (b) postnatal complications, e.g. sepsis, jaundice, seizures, etc. (c) intensive care admission, and (d) day of the discharge from the hospital.

8. Dietary history aims to differentiate dietary malnutrition from organic causes of failure to thrive. Focus of this history must be relevant to the age, with basic information about: (a) feeding in early infancy, (b) complimentary feeding or weaning, and (c) present diet with special reference to caloric and protein intake. Important aspects of dietary history are as follows:

- *In infants below 6 months*, concentrate on the history related to early infant feeding with special emphasis on *Type of feeding*, e.g. breastfeeding or/Top feeding, *appropriateness* of breastfeeding practices (Ch 5.2.4), *problems encountered* during breastfeeding (Ch 5.2.5), *reasons for* top-feeding, if applicable, and *mode of top-feeding*, e.g. bottle.
- *In children from 6 months-2 years*, concentrate on the history related to complimentary feeding along with a quick review of early infant feeding, with special emphasis on *age* of introducing weaning foods, *adequacy* of weaning in terms of quality and quantity, *problems* encountered during weaning and whether breast-feeding has been continued. (Ch 5.5).
- *In children > 2 years*, concentrate on the current food intake in terms of proteins and calories apart from a quick review of the early infant feeding and weaning. (Ch 5.7 - 5.8)
- Dietary intake must be calculated by 24-hour recall method, for two different time-periods to assess the cause-effect relationship between diet and disease – in 24 hours *before* recording the history and 24 hours *before* the onset of present illness.
- Post-history, *actual dietary intake* must be calculated by using nutritional value of common Indian feeds **(Tables 5.9–5.10)** and compared with reference nutritional requirements for the chronological age, predominantly for energy and proteins **(Table 5.1)**, to find out the deficit, if any. **Table 30.5** provides a simple, back-of-the-envelope calculation to assess nutritional requirements for proteins and calories in children, using expected weight.
- Information must also be obtained regarding staple diet, intake of micronutrient-containing foods, general appetite and food-fads or intolerance.

TABLE 30.5 : Quick calculation of approximate energy and protein requirements

Energy (by Wt*)	< 10 Kg	=	100 cal/ kg
	10-20 Kg	=	1000 cal + 50 cal/kg >10 kg
	> 20 kg	=	1500 cal + 20 cal/kg >20 kg
Proteins (by Wt*)	< 10 kg	=	2 gm/kg
	> 10 kg	=	1.5 gm/kg (Minimum 20 gm)

*expected weight for age

9. Immunization history aims to evaluate the role of vaccine-preventable diseases or adverse reactions to vaccines in causation of present illness. It should be cross-checked with records, if available. Main emphasis should be to record the receipt of vaccines as per national immunization schedule, to be followed by additional vaccines **(Tables 9.3 and 9.4)**. Find out about any adverse event following a vaccine dose or any relationship with presenting illness.

10. Developmental history is age-dependent, more relevant in cases with neurological or developmental problems or the risk-factors for the same, e.g. perinatal insult. Important aspects of the developmental history are as follows:

- Developmental history must record achievement of various milestones in four major fields - *Gross motor, Fine motor, Social-adaptive and Language,* along with the age of attainment **(Table 30.6)**.
- Age of attainment must be compared with expected norms, with due consideration for normal physiological variations.
- In cases with presenting complaints suggestive of neurodevelopmental problems or risk factors, development history must include details about all major milestones in different fields, starting from early neonatal period to get an idea about the age from which milestones began to falter.
- In other cases, begin with milestones that the child should have achieved by present chronological age. *If yes*, than the development is most likely normal and further enquiry about earlier milestones is probably unnecessary as the general order of the appearance of milestones is fairly constant. *If no*, find out the last major milestone achieved in each field by going in backward order of development to assess the developmental age.
- In cases with delayed milestones, assess whether milestones are uniformly delayed in all the fields

TABLE 30.6: Developmental history: Key milestones in different fields

Age	*Gross motor*	*Fine motor*	*Social-Adaptive*	*Linguistic*
6 wks	Lifts chin	Fixes vision	Social smile (6 weeks)	Turns head to sound
3 mo	Neck holding	Eyes follow moving objects	Recognizes mother	Turns to sound
4 mo	Rolls over	Reach-out to objects	Laughs loud	Cooing sounds
6 mo	Sits with support	Transfer of objects	Stranger anxiety	Mono-syllables
9 mo	Crawls	Pincer-grasp	Waves bye-bye	Bi-syllables
	Sits without support			Responds to name
12 mo	Stands without support	Releases objects on request	Plays/throws ball	2 meaningful words
15 mo	Walks, creeps upstairs	Tower of 2 cubes	Point to objects	Jargon speech
		Turns 2 pages at a time		
18 mo	Runs, walks upstairs	Scribbles	Bladder control (day)	8 meaningful words
24 mo	Jumps,	Tower of 6 cubes	Points 3 parts of doll	Sentence of 2–3 words
	Walks downstairs	Turns one page a time		
30 mo	Kicks a ball	Draws line	Knows name/gender	Ask questions
36 mo	Rides tricycle, hops	Draws circle	Recite rhymes	Narrate experiences
		Makes bridge (3 cubes)	bladder control (night)	
4 yr	Hops on one foot	Draws cross, bridge	Group play	Sing songs, stories
5 yr		Triangle	Help in household work	Asks meaning of words

(global delay). Isolated delay in one or two fields *(developmental dissociation)* is usually due to non-neurological causes, e.g. hearing impairment (delayed language), severe malnutrition (gross motor delay).

- In cases with abnormal development, find out if the some milestones were never gained *(developmental delay)* or if they have been lost after the initial achievement *(developmental regression)*. Regression of milestones is an important clue to neurodegenerative disorders.
- In school-going children, academic performance and social interaction with other students are also useful indicators of development.

11. Personal history is more important in older children and adolescents and must include information about: *(a) eating habits and food fads, (b) bladder and bowel control, (c) sleeping patterns, (d) temperament and behavioral problems, and (e) menstrual history in girls*.

12. Socioeconomic history aims not only to identify the risk factors for causation of disease but also to decide appropriate diagnostic, therapeutic and rehabilitative interventions, acceptable and affordable by parents. Three important components of social history include parental—(a) *educational status*, (b) *occupation, and* (c) *income*. *Modified Kuppuswami classification* **(Table 30.7)** can be used for more objective assessment of socioeconomic status, though not necessarily required in all cases.

13. Environmental history must search for risk factors in various components of indoor and outdoor environment including: (a) *Overcrowding*, as assessed by the size and

TABLE 30.7: Modified Kuppuswami classification

Variable score	
A. Educational status	
1. Professor or honors	7
2. Graduate or postgraduate	6
3. Intermediate or post-high school	5
4. High school	4
5. Middle school	3
6. Primary school	2
7. Illiterate	1
B. Occupational status	
1. Professional	10
2. Semi-professional	6
3. Clerical, shop owner, farmer	5
4. Skilled worker	4
5. Semi-skilled worker	3
6. Unskilled worker	2
7. Unemployed	1
C. Monthly family income (Rs)*	
1. ≥ 249044	12
2. 124489-249043	10
3. 93381-124488	6
4. 62273-93380	4
5. 37325-62272	3
6. 12445-37324	2
7. ≤ 12445	1
Socio-economic classification	
Upper (I)	26–29
Upper-middle (II)	16–25
Lower-middle (III)	11–15
Upper-lower (IV)	5–10
Lower (V)	< 5

*Adjusted for inflation 2023

number of rooms in house *vis a vis* the family size, (b) *air-quality* as assessed by ventilation, pollution by cooking fuel, passive smoke, construction activity or chemic/toxic fumes, (c) *water-quality* as assessed by questions related to the source, storage and purification method for drinking water, and (d) *general sanitation* as assessed by questions related to the hygiene awareness and practices, specially during food preparation/consumption and excreta disposal.

Analysis: At the end of this session, history should be re-arranged and analysed in details to identify the:

- Organ or system involvement, as far as possible;
- Probable etiology of illness, e.g. infection, metabolic, traumatic, etc.
- Nature of disease process, e.g. acute, chronic, progressive, static, etc.
- Severity of the disease process.
- Focus of examination and investigations.

Analysis and interpretation of common symptoms and related information obtained during the history has been discussed in relevant chapters of this book.

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CHAPTER

31

General Physical Examination

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Physical examination of a young child is a skill that comes with experience. While broad principles and format of examination in children is same as in adults, following differences are noteworthy:

- The Child is usually an unwilling subject, who can disrupt the examination at any time and rarely allow the examination in an orderly sequence.
- Anxious parents present at the time of examination may interfere in the process with their own concerns, emotions and priorities.
- History is often imprecise and incomplete, making physical examination more important to arrive at a diagnosis.
- Examination needs to be modified in context of the age, in term of sequence, methodology and interpretation. It also includes additional components of anthropometry and developmental assessment.

This chapter deals only with *general* physical examination of a child beyond the neonatal period, as examination of various systems has been discussed in respective chapters. Examination of a newborn has been discussed separately in Chapter 12.5.

General Considerations

Physical examination of children needs comfortable environment, good rapport, age-appropriate techniques and correct interpretation of findings. Some important prerequisites for good physical examination are as follows:

- **Setting:** Child should be examined in a comfortable and pleasant environment to ease the anxiety, with due regard to the privacy. Older or adolescent girls must be examined only in presence of a female nurse or relative.
- **Rapport-building:** Development of good rapport with the child is vital for successful physical examination and useful strategies include: (a) greet and introduce yourself, (b) address the child with name, (c) let the child play with examining instruments and offer some chocolate, etc., if possible, (d) allow the parents to be present and converse with them lightly while observing the child, without staring at him/her, (e) avoid unnecessary and complete removal of cloths, (f) explain the procedure to older children or parents, (g) converse in a friendly manner while examining the child, to distract him/her.
- **Position:** Newborns, young infants (<3 months) and older Children (>3 years) can usually be examined on examination table - the best place to do so. However, older infants or toddlers are more comfortable in mother's lap or in standing position and the position of examination must be modified according to their comfort.
- **Examination-kit and hygiene:** All essential equipments, e.g. stethoscope, torch, measuring tape, spatula, thermometer, weighing scale and development assessment tools must be in place, in clean, working condition, to avoid unnecessary interruptions during the examination session. It is advisable to have few clean bright-color toys, which can be offered to distract the child. Examiner's hands should be washed thoroughly and warmed by rubbing against each other, before touching the child.
- **Methodology:** *Observation is the most important step in the examination*, which should begin at the level of first contact with the child and must continue throughout the history-taking and examination process. It is always preferable not to touch the young child if the desired information can be obtained by observation. Palpation must be soft and gentle, percussion to be avoided in possible and auscultation must be synchronized with respiratory phases in a crying child.
- **Order and sequence**: While broad protocol of examination in children is nearly same as in adults, the order of assessment must be modified according to the child's age, level of cooperation and the real need to get that information. C*hild is the king* and examiner must try to get as much information as possible without annoying him/her. In a cardiac case, auscultation may be done prior to the palpation or percussion. Scary

or painful procedures, e.g. examination of throat or reflexes must be postponed till the last, aborted at the first hint of child's discomfort. It is usually impossible to complete thorough physical examination of a child in one sitting.

- **Interpretation:** Examination findings in children must be interpreted in context of their age as what is abnormal in adults may be normal or physiological in young children, e.g. jaundice in a newborn, extensor planters in infants, enlarged tonsils and lymph nodes in school-children, etc.
- **Documentation** is essential to maintain records for future reference and legal purpose, signed and dated by examiner. All findings must be recorded as soon as possible, preferably in a pre-structured format. Figures and diagrams may be used to depict findings like rash, etc.
- **Closure:** At the end, examiner must discuss essential observations with the parents, but the opinion regarding diagnosis or outcome must be reserved, unless one is sure about it. It is also preferable to have light chit-chat with the child to set the stage for further interaction. Child may also be praised and rewarded with chocolate, etc. for cooperation.

Components

General examination in a child may be broadly divided into six components, as follows:

A. General appearance
B. Vital signs
C. General markers of the disease
D. Anthropometry
E. Head-to toe examination
F. Developmental assessment, if required.

A. General appearance not only points towards the severity of illness and urgency to manage but also assists in the differential diagnosis. However, looks can be deceptive and the reliability of this information depends on the experience of observer.

Assessment of general appearance includes assessment of: *(a) built, (b) mental state, (c) posture, (d) movements, and (e) cry*. Other important observations, e.g. abnormal odor (e.g. in poisonings) or sounds (e.g. stridor, wheeze, etc.) must also be recorded.

Table 31.1 provides broad terms used to describe common general appearance and their clinical interpretations. Some characteristically abnormal postures have been shown in **Fig. 31.1**.

B. Vital signs: Assessment of vital signs must receive the top priority in general examination in sick children, to identify the need for immediate attention (*emergency triage*). Important vital signs include: *(a) body temperature, (b) pulse or heart rate, (c) respiration, (d) blood pressure, and (e) capillary refill time*; which should be interpreted in

TABLE 31.1: Components of general observation

Built
- Wasted..... *(Malnutrition, FTT)*
- Obese..... *(Nutritional, Endocrinal)*
- Stunted..... *(Chronic FTT)*

Mental state
- Apathetic or Depressed ...*(Illness, Behavioral)*
- Drowsy, Stupor, Comatose.... *(Severe Illness, CNS)*
- Irritable, restless, Delirious.... *(Hyperpyrexia, CNS)*
- Anxious and Scared.... *(Rabies, child-abuse)*

Posture preferred
- Squatting.... *(Cyanotic CHD)*
- Propped-up.... *(CCF, severe ascites)*
- Stooping-forward... *(Asthma)*
- Curled-up... *(Abdominal pain)*
- Lateral Decubitus... *(Local pain)*
- Decerebrate or Decorticate... *(CNS lesion)*
- Pithed-frog position.... *(Floppy child)*
- Scissoring..... *(Cerebral palsy)*
- Opistotonus.... *(Tetanus)*

Limb movements
- Unilaterally Restricted.... *(Paralysis, pain)*
- Abnormal.... *(Seizures, Extrapyramidal lesions)*
- Abnormal Gait ***(Table 18.1)***

Cry
- High-pitched.... *(Raised ICT, Kernicterus)*
- Hoarse.... *(Laryngitis, Hypothyroidism)*
- Intermittent.... *(Colic, Insect bite)*
- Inconsolable.... *(Severe pain or discomfort)*
- Cat-like cry.... *(Cri-do-chat syndrome)*
- Goat-like Bleat.... *(Infantile tremor syndrome)*

FTT: Failure to thrive, **ICP:** Intracranial pressure.

Fig. 31.1: Common characteristic postures in disease: (A) Decerebrate posture; (B) Scissoring; (C) Opisthotonus; (D) Frog-like posture.

TABLE 31.2: Normal range of vital signs in children

Age	*HR (min)*	*RR (min)*	*BP* (mmHg)*
0–3 mo	100–150	35–55	65/45
3–6 mo	90–120	30–45	70/50
6–12 mo	80–120	25–40	80/55
1–3 yr	70–110	20–30	90/55
3–6 yr	65–110	20–25	95/60
6–12 yr	60–95	14–22	110/60
>12 yr	55–85	12–18	110/65

*Lowest of the range for systolic/diastolic BP.

context of the age, considering physiological variations **(Table 31.2)**.

Pulse must be assessed by palpation of a peripheral vessel using three-fingers—Index, middle and ring finger, for: *(a) rate, (b) rhythm, (c) volume, (d) character, and (e) radio-femoral delay.*

While right radial artery is usually palpated for this purpose due to ease of examination and being in direct continuation of left ventricular outflow, other vessels should also be palpated, specially – the right carotid artery for volume, femoral artery for radio-femoral delay and distal vessels, e.g. Dorsalis pedis artery for peripheral block or thrombosis in sick children. Pulse rate must be counted for minimum one minute, though in emergency cases, pulse count for 15-30 seconds may be relied upon, multiplied by 4 or 2 respectively. In young infant, pulse may be difficult to assess and heart rate may be counted by auscultation.

Pulse rate or heart rate varies with age **(Table 31.2)** and normal pulse is in sinus rhythm, good-bounding volume and no radio-femoral delay. For further details, *see* Ch 17.2.

Respiration must be observed when the child is quite and not agitated, preferably before touching the child. A young child may be observed in the mother's lap. Respiration should be assessed for: *(a) rate, (b) rhythm, (c) type, (d) work of breathing, and (e) presence of adventitious sounds.*

Respiratory rate varies with age **(Table 31.2)**. Normal respiration is regular, thoraco-abdominal (abdomino-thoracic in infants), effortless without use of accessory muscles and no adventitious sounds. For further details, *see* Ch 16.2.

Assessment of oxygen saturation by using hand-held pulse oximeter is advisable, if possible, in obviously dyspneic children. SaO_2 of <93% in children and <90% in newborns indicates significant hypoxia.

Body temperature is usually recorded in oral cavity in older children and axilla or groin in younger children using mercury-free digital thermometer. Rectal temperature is rarely recorded at present and temperature recorded in ear canal by infrared thermometer or over forehead by thermo-sensitive strips, is unreliable.

TABLE 31.3: Descriptive terms used in relation to body temperature

- Hypothermia (<35°C)
- Cold stress (<36.4°C)
- Normal (36.4–37.4°C)
- Fever (>38°C)
- Hyperpyrexia (>40°C)

Skin temperature must be recorded by cleaning the site and placing the thermometer bulb snugly at desired site and flexing the arm against the chest (Axilla) or thigh against the abdomen (Groin), for at least 2 minutes. *Oral temperature* must be is recorded by placing the thermometer under the tongue and asking the child to close the mouth and breath through the nose. Oral temperature should not be recorded soon after any hot or cold drink.

Oral temperature is ~0.4°C lower than rectal temperature and ~0.4°F higher than skin temperature. Temperature criteria for commonly used descriptive terms in relation to body temperature are given in **Table 31.3**. For further details, also *see* Chapters 10.1 and 12.12.

Blood pressure (BP) must be recorded using appropriate cuff-size, by auscultatory method and using a mercury free sphygmomanometer, taking first and fifth Korotkoff sound as indicator of systolic (SBP) and diastolic (DBP) pressure respectively.

In infants, *Flush method* may be used to determine the mean BP. For further details *see* Ch 17.12. Normal BP varies with age as given in **Table 31.2**, though can also be roughly calculated as:

SBP = 90 + (Age in yr × 2) mm Hg

DBP = 55 + (Age in yr × 2) mm Hg

Normal pulse pressure (SBP-DBP) is <40 mm Hg. SBP is ~5–10 mm less during inspiration than in expiration. BP is also relatively higher in lower limbs (~10 mm) than in upper limbs. For further details, *see* Ch 17.12.

Two other important signs may also be checked at the time of recording BP in selected cases, i.e. *Hess test* for suspected purpura (Ch 19.10) and *Trousseau* sign for suspected Tetany (Ch 7.4).

Capillary refill time (CRT) indicates state of peripheral perfusion and must be checked in all sick children by pressing the thumb over a bony prominence, e.g. sternum/forehead for 5 seconds to blanch the skin. Time taken to regain the color (flush) of skin after pressure is removed denotes CRT, which should not exceed 3 seconds. Prolonged CRT indicates impending or established circulatory shock.

C. General markers of the disease: Many clinicians prefer to look for some important markers of the diseases, after the assessment of vital signs but before

Fig. 31.2: **Common clinical indicators of disease: (A) Icterus; (B) Cyanosis; (C) Clubbing; (D) Dehydration (Turgor); (E) Edema; (F) Lymphadenopathy.**

exhaustive head-to-toe examination, to accelerate the process of differential diagnosis. Some important markers of disease in children include presence of: *(a) pallor, (b) cyanosis, (c) clubbing, (d) icterus, (e) edema, (f) lymphadenopathy, and (g) dehydration* **(Fig. 31.2)**.

Pallor, indicative of anemia, must be assessed over palpebral conjunctiva, oral mucus membrane and palms, though severe pallor may be obvious over skin. It should not be confused with peripheral pallor due to vasoconstriction in shock or on cold exposure, which can be improved by rubbing. Pallor may be graded as *Mild* (limited to mucus membranes), *Moderate* (visible on skin/palms) and *Severe* (paleness of palmer creases). For further details and differential diagnosis, *see* Ch 19.2 and 29.1.

Cyanosis, indicative of cellular hypoxia, must be assessed over nails for peripheral cyanosis and lips/tongue for central cyanosis, as bluish discoloration. Peripheral cyanosis is usually transient, due to local vascular stasis, e.g. cold or shock, and disappears rapidly on rubbing of the affected part to improve the circulation. Central cyanosis may be of pulmonary and cardiac origin, which can be further differentiated by *Hyperoxia test*. Cardiac cyanosis does not improve with oxygen. Differential cyanosis is limited only to either upper or lower limbs, indicative of right to left shunt at the level of patent ductus arteriosus. For further details and differential diagnosis, *see* Ch 17.2.

TABLE 31.4: Grades of severity in clubbing

I.	Softening of nail bed on palpation
II.	Obliteration of angle at nail bed (Schamroth sign)
III.	Increased horizontal or vertical curvature of nails (Parrot-beak or Drum-stick appearance)
IV.	Hypertrophic osteoarthropathy (painful swelling of the hands/wrist)

Clubbing, i.e. may be easily visible as bulbous enlargement of the nail-beds at all fingers, due to due to vascular proliferation and interstitial edema of underlying structures. However, detection of early clubbing needs palpation of the nail bed for softening or use of *Schamroth sign*, i.e. disappearance of the normal diamond-shaped gap, when dorsal surfaces of two opposite terminal phalanges are brought together (*see* **Fig. 17.7)**. Clubbing of the toes may be normal and misleading in bare-foot walkers. Severity of the clubbing may be graded as in **Table 31.4**. For further details and differential diagnosis, *see* Ch 17.2.

Icterus, presents as yellowish discoloration of skin and mucus membranes. While it is clinically visible only when serum bilirubin levels exceed 2 mg/dl and first seen over the Sclera. More severe icterus may also be visible on the palate, undersurface of tongue and even on skin. Icterus over the sclera should not be confused with muddy sclera due to prolonged dust/smoke exposure or vitamin A deficiency. Color of the icterus may help to differentiate hemolytic (lemon-yellow) and hepatic (Golden-yellow) etiology. For further details and differential diagnosis, *see* Ch 15.3.

Edema denotes accumulation of excess fluid in interstitial spaces, best assessed by pressing over the suspected site for 5 seconds, leading to formation of a pit (Pitting edema). Generally, it is checked over the shins, ~2 cm above the medial malleolus. However, it must also be checked over the sacral region in young infants and bed-ridden patients, as most dependent part. The term *Minimal edema* is used when it can be elicited only after >20 seconds of pressure. Edema may be non-pitting in cases of myxedema or lymphatic obstruction. For further details and differential diagnosis *see* Ch 7.1.2.

Lymphadenopathy may be indicative of local or systemic pathologies, though nodes are physiologically enlarged

Fig. 31.3: **Palpation of cervical lymph nodes: (A) From behind; (B) From front.**

in early school children due to normal lymphoid growth. Examination of lymph nodes involves evaluation of various groups, e.g. cervical, axillary and femoral nodes for: *(a) size, (b) location, (c) consistency, (d) tenderness, (e) secondary changes*, e.g. *matting or sinus formation, and (f) inflammatory focus in the draining area*.

Cervical group is best palpated from behind with child whose neck is semi-flexed and tilted on the opposite side **(Fig. 31.3)**. All cervical nodes, including submental, submandibular, preauricular, postauricular and occipital nodes of horizontal chain, superficial and deep cervical nodes of vertical chain, lateral cervical nodes in posterior triangle of neck and supraclavicular nodes, must be examined systematically in a sequence. *Axillary nodes* are best palpated by inserting the fingers in axilla with patient's arm slightly abducted. This group includes apical, anterior, posterior, medial and lateral axillary nodes. *Lymph-nodes of <1 cm in size, discrete, mobile and non-tender are usually physiological and not significant.* For further details and differential diagnosis, *see* Ch 19.17.

Dehydration presents with constellation of many clinical indicators, though most important examination findings include: (a) sunken eye balls, (b) depressed anterior fontanel, if open, and (c) loss of skin turgor. *Skin turgor* may be assessed by pinching and lifting the skin and subcutaneous tissue, usually over abdomen, for few seconds. On releasing the pinch, normal skin recoils immediately and slow or delayed recoil indicates loss of skin turgor. Assessment of turgor may be misleading in obese or severely malnourished children. For further details, *see* Ch 7.1.3.

D. Anthropometric parameters indicate status of growth, which can be affected by many factors, including disease. While the choice of the parameter to be recorded in a child depends on the expected problem, three basic anthropometric parameters must be recorded in all cases: *(a) weight, (b) height, (c) head circumference*. Additionally, *mid-upper arm circumference* (MUAC) must be recorded in children from 1-5 years, *Body proportion parameters* (*Upper segment: Lower segment ratio or Arm span*) in children with abnormal stature and *Body mass index* (BMI) in overweight children.

Anthropometric parameters recorded in an individual case must be compared with reference norms for the corresponding age and sex, using WHO growth norms/charts (<5 years) or IAP growth norms/charts (>5 years), as discussed in Ch 2.4. Actual values beyond the ± 2 SD (<3rd or >97th percentile) of the corresponding normal values are considered as abnormal. For the sake of simplicity, actual values may also be denoted as percentage of normal values for interpretation.

For further details and methodology to record anthropometric parameters, see Ch 2.5.

Body proportions need to be assessed only in children with short or tall stature, using two parameters – *Upper segment: Lower segment ratio* (US:LS), also termed as *CR:RH ratio* (crown-to rump and rump-to heal length) and *Limb span*. US:LS ratio is best calculated by recording the sitting height (US) and deducting in from Standing height (LS). Limb span is recorded directly as the distance between tips of middle fingers of outstretched hands. For further details, *see* Ch 2.3.1.

Body mass index needs to be calculated only in apparently overweight child as *weight in kg/ (Height in meter)*^{2} For further details, *see* Ch 3.2.

Other anthropometric parameters, e.g. *chest circumference* or *skin-fold thickness* are of limited value in clinical practice, discussed in Ch 2.3.1.

E. Head-to-toe examination is the systematic and exhaustive evaluation of a child to search for diagnostic clues regarding the presenting illness and any coexisting health problem. Following discussion is limited to the common and important physical findings, though the actual assessment should be more exhaustive. Broadly, each organ should be examined for: *(a) dysmorphic features, (b) external injury, (c) infection, and (d) medical disease*, with due consideration for normal physiological variations in a growing child.

Head should be *inspected* for the shape, *palpated* over fontanels, sutures, and vault, *percussed* for Macewen sign and *auscultated* for bruit. Large head must also be tested for *Transillumination*. Size of the head is recorded as head circumference, discussed earlier.

On inspection, head is proportionately larger than body in infancy with mild frontal bossing. Some common abnormalities of head are shown in **Fig. 31.4**.

Fig. 31.4: Common head abnormalities: (A) Microcephaly; (B) Craniosynostosis; (C) Hydrocephalus; (D) Frontal bossing.

On palpation, Anterior fontanel is open (2 × 2 cm) at birth but closes gradually over next 18 months, posterior fontanel may admit little finger at birth but definitely closes by 3 months, and sutures are palpable but not prominent. *Craniotabes*, i.e. Ping-pong ball like softening of skull bones felt on pressure over parietal region is normal in preterms and young infants < 3 months.

On percussion, *Macewan sign* is elicited by gentle tapping over the sutures on one side and hearing on the opposite side directly or by stethoscope **(Fig. 31.5)**. Presence of typical *crack-pot* sound indicates sutural gap, seen in raised intracranial pressure. It may be normal in first 18 months, till fontanel closes.

On auscultation, cranial bruit may be normal in 15% children.

Transillumination is elicited in a dark room, by pressing the flash-light over frontal and occipital region. A rim of tranillumination exceeding > 2.5 cm in frontal region and >1 cm in other parts of scalp is abnormal.

Table 31.5 enlists important head abnormalities in children with common differential diagnosis.

Scalp must also be inspected for quantity and pigmentation of hair, infection, e.g. Lice and disease, e.g. Seborrhic dermatitis, palpated for the easy pluckability of hair and any swelling, e.g. hematoma. Distended scalp veins may indicate hydrocephalus.

Fig. 31.5: Macewan sign.

TABLE 31.5: Examination of the head

Small head	Microcephaly craniosynostosis
Large head	Hydrocephalus, macrocephaly
Abnormal shape	Craniosynostosis (Fig. 23.1), swelling
Frontal bossing	Rickets, hemolytic anemia
Wide-open AF	Rickets, hydrocephalus
Depressed AF	Dehydration
Bulging AF	Raised intracranial pressure
Wide-open PF	Hypothyroidism
Wide sutures	Hydrocephalus
Prominent sutures	Craniosynostosis
Craniotabes	Rickets, preterms
Macewan sign +ve	Raised ICP (>18 month)
Transillumination	Subdural effusion, hydrocephalus
Cranial bruit	Intracranial vascular malformations

Face must be inspected for disease-specific facies **(Fig. 31.6)**, minor dysmorphism (low-hair line, long/short philtrum), expressions, asymmetry of movements, injury, infection or disease. Mandible must be also examined for size (prognathia, retrognathia) and movements (lock jaw). Facial movements may be apparently asymmetrical in facial palsy.

Eyes must be examined for *Location* (hypertelorism or hypotelorism), *Size* (microphthalmia, proptosis), *Shape* (mongoloid or anti-mongoloid slant) *Dysmorphism* (epicanthic folds), *Eyelid movements* (ptosis), *Extraocular movements* (skew deviation, gaze palsy), *Intraocular movements* (nystagmus, strabismus) and other *abnormal findings*, e.g. injuries, infections or diseases involving lids, lacrimal system, conjunctiva, cornea, uveal tract and pupils. Lens should be examined for cataract or

Fig. 31.6: Characteristic facial features in common childhood diseases: (A) Down syndrome; (B) Mucopolysaccharidosis; (C) Cleft lip; (D) Cretinism; (E) Moon face (Cushing syndrome); (F) Hemolytic face; (G) Marasmus; (H) Kwashiorkor; (I) Facial palsy; (J) Adenoid facies; (K) Trismus (Tetanus); (L) Retrognathia.

cat-eye reflex followed by *fundus* examination in all cases with suspected neurological disorder. Careful eversion of the upper lid **(Fig. 31.7)** may be required in cases of suspected foreign body.

Visual acuity must be tested in all cases by age-appropriate methods **(Table 26.13)**. Examination of color vision and field of vision is required only in selected cases. Extraocular movements must be assessed by asking to follow the examiner's instructions, though Doll's eye maneuver may be required in unconscious cases. Strabismus can be checked by *Hirschberg test*. Physiological squint is common in infancy. Cover test is used to differentiate paralytic from non-paralytic squint. Nystagmus, if present, must be checked for the direction.

For further details regarding common ophthalmic and visual disorders, *see* Ch 26. Some common ocular abnormalities are shown in **Fig. 31.8**.

Ears should be *inspected* for *Location* (low-set), *Dysmorphism* (microtia, bat-ears, pre-auricular tags) and *Discharge* and *Palpated* for tragus tenderness. Otoscopic

Fig. 31.7: **Eversion of the lid.**

Fig. 31.8: **Common ocular abnormalities: (A) Proptosis; (B) Microphthalmia; (C) Cat eye reflex (Cataract); (D) Hordeolum externum.**

examination is necessary in all cases with otic symptoms or hearing impairment. *Low-set ears* with helix below the horizontal line passing through medial canthii **(Fig. 31.9)**, are common in many genetic disorders, e.g. Down syndrome, Turner syndrome and Di George syndrome.

Dysmorphic external ear may be associated with genetic or congenital abnormalities, e.g. microtia in goldenhar

Fig. 31.9: **Important ear abnormalities: (A) Low-set ears; (B) Anotia; (C) Preauricular tag; (D) Bat ears.**

or Treacher-Collin's syndrome, Bat-ears in Fragile-X syndrome, pre-auricular tags in renal anomalies and hairy-pinna in infants of diabetic mother.

Tragus tenderness, i.e. excessive cry when tragus is pressed, is a reliable sign of painful ear-canal conditions, e.g. furuncles or ear-drum inflammation, e.g. otitis media, in young infants.

Formal hearing assessment is indicated in cases with suspected deafness or delayed language development **(Table 3.14)**.

For further details regarding common ear problems and hearing disorders, refer Ch 16.5.4 and Ch 3.8 respectively. Some common ear abnormalities are shown in **Fig. 31.9**.

Nose should be inspected for *dysmorphic* features, *infection*, *injury*, *discharge* and *stigmata* of allergic rhinitis, e.g. shiners, wrinkles or rabbit-nose. Nasal cavity must also be examined with a speculum, specially in cases with suspected *foreign body*, persistent nasal block/discharge (polyps, deviated nasal septum) or epistaxis. Patency of the nasal passage, e.g. in unilateral choanal atresia can be tested by spatula test.

Fig. 31.10: **Common nose abnormalities: (A) Depressed nasal bridge; (B) Beak shaped nose.**

Dysmorphic features may be normal or associated with other genetic or developmental anomalies, e.g. depressed nasal bridge in Down syndrome or Hurler syndrome, beaked nose in Apert syndrome or progeria, rudimentary or upturned nose in holoprosencephaly and hypoplastic alae nasi in infants of diabetic mother **(Fig. 31.10)**. For further details regarding common nasal disorders, refer to Ch 16.5.1.

Oral cavity must be inspected externally for *Dysmorphic features*, e.g. cleft-lip, *Symmetry* during cry (facial palsy, congenital) and *Lip* lesions (cheilosis, angular stomatitis) and swelling of the salivary glands. Lifting of the ear pinna is an important sign of parotitis in mumps.

Oral cavity must be inspected under bright torch light for *Orodental hygiene*, *Oral mucosa* (cyanosis, dryness, Ulcers, Thrush, Koplic spots) *Tongue* (Color, Coating, symmetry, movements, ulcers) and *Teeth* (number, caries, gingival bleed/hypertrophy). Beefy red or Strawberry tongue indicates Riboflavin deficiency and Kawasaki disease, respectively.

For further details regarding common oro-dental disorders, refer to Ch 14.5. Some common oral cavity abnormalities are shown in **Fig. 31.11**.

Throat examination is often scary, and may be deferred till the end of physical examination. In an uncooperative child, it may require proper restraining in sitting or lying down position with neck extended partially with use of a spatula. Crying usually helps to see the throat, which should be examined for congestion, membranes **(Fig. 31.12)**, tonsillar enlargement, uvular position, movement of soft palate and posterior pharyngeal wall reflex.

Throat should not examined in suspected croup till resuscitation facility is available. For further details regarding common Throat disorders, refer to Ch 16.5.2.

Neck must be examined for the length (Short, web neck in Turner syndrome, Klippel-Feil syndrome **(Fig. 31.13)**, position (Torticolis), swelling (goiter, hygroma in midline, branchial cysts laterally), movements (neck rigidity) and prominent of veins or visible pulsations (dancing carotids).

Fig. 31.11: **Common oral abnormalities: (A) Cleft palate; (B) Caries; (C) Thrush; (D) Strawberry tongue.**

Fig. 31.12: **Diphtheria membrane.**

Fig. 31.13: **Neck abnormalities: (A) Webbing (Turner syndrome); (B) Klippel-Feil syndrome.**

Jugular venous pressure (JVP) must be assessed in semi-reclining position and measured correctly **(Fig. 17.6)**. It may be difficult to appreciate in young children, due to shorter neck and struggling child. Hepato-jugular reflux should also be checked in cases with suspected heart disease.

Skin must be *inspected* after proper unclothing the baby, for pigmentation, rash, bleeding, e.g. purpura, malformations, e.g. nevi, Infections and other diseases; and *palpated* for texture, turgor, edema and deeper lesions, e.g. nodules. Hypertrichosis may be abnormal. Evaluation of palmer creases, i.e. *Dermatoglyphics*, may be useful in suspected genetic disorders, e.g. Down syndrome.

Rashes must be described according to the morphology, distribution, pruritis and secondary changes **(Table 25.1)**. Use of a magnifying glass may be necessary to confirm the subtle findings. Interdigital region must be examined carefully in case of suspected scabies. Specific signs, e.g. *dermatoglyphism* or *Nikolsky sign* must be assessed in relevant cases. Some characteristic rashes have been shown in **Fig. 31.14**. For further details and figures regarding common skin disorders, refer to Ch 25.

Nails must be inspected for *Color* (pallor, cyanosis, dyspigmentation), *Deformity* (platonychia, koilonychia, *Beau* lines), *infection* (paronychia, onychomycosis) and palpated for *clubbing* and *brittleness*. For further details regarding common nail disorders, refer to Ch 25.11.4.

Genitals must be examined with due consideration to privacy and only in presence of a female relative in case of girls. These organs should be assessed for any *morphological* abnormality, e.g. ambiguous genitals, micropenis and undescended testes in males, clitoral hypertrophy in females, along with any *discharge, infection or sign of sexual abuse*. Some common external genital abnormalities are shown in **Fig. 31.15**. *Sexual maturity rating* (SMR) must be assessed in all school children **(Table 13.2)**.

Back and spine must be examined for any *deformity, skin lesions, swelling and tenderness*. Deformities, i.e. kyphosis or scoliosis, may be congenital or acquired, e.g. Pott's spine. Presence of a non-specific skin lesion, e.g. dimple, sinus or tuft of hair must alert about the possibility of underlying neural tube defects. Bedsores are common in chronic debilitated patients. A midline swelling may be due to meningocele. Localized tenderness over spine may indicate deeper trauma or inflammatory lesions, e.g. Pott's spine. Some common Spinal abnormalities are shown in **Fig. 31.16**. For common Spinal problems, refer to Ch 23.2.3.

Limbs must be examined for any *malformations, deformity, swelling, tenderness or restriction of movements*. Any unusual or asymmetrical hypertrophy or atrophy

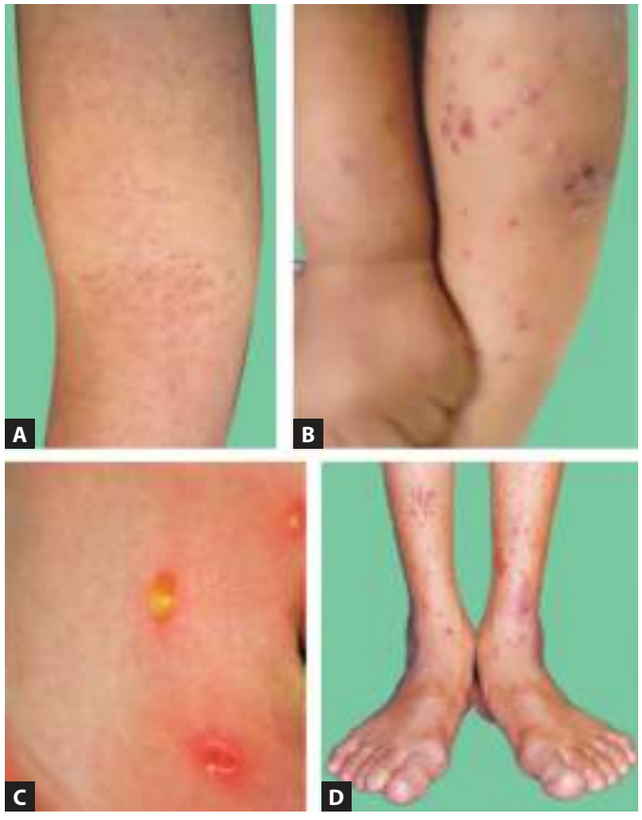

Fig. 31.14: **Skin rashes: (A) Macular rash; (B) Papular and pustular rash; (C) Pustule; (D) Purpuric spots.**

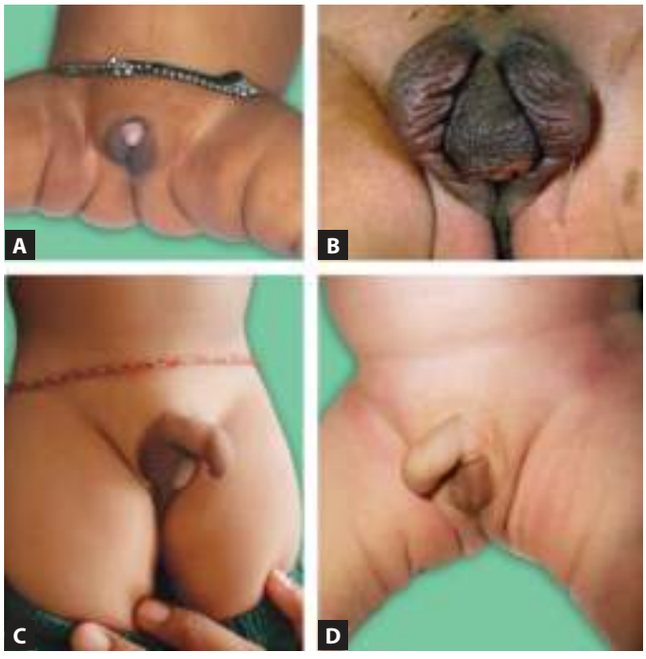

Fig. 31.15: **Common genital abnormalities: (A) Ambiguous genitalia; (B) Clitoral hypertrophy; (C) Hypospadias; (D) Cryptorchidism.**

Fig. 31.16: **Spinal abnormalities: (A) Kyphosis; (B) Bed sores; (C) Sacral dimple; (D) Tuft of hair over spine.**

Fig. 31.17: **Common bony abnormalities: (A) Knock knee; (B) Bow legs; (C) Arthritis; (D) CTEV.**

of the limb muscles may also indicate underlying neuromuscular disorders. An abnormal gait or avoidance/paucity of a particular limb movement may be due to neuromuscular causes (paralysis) or painful limb lesions (pseudoparalysis).

Some common orthopedic abnormalities in children are shown in **Fig. 31.17**. For common orthopedic limb problems, refer to Ch 23.2.2.

Bones and joints, must be examined for any *malformations, deformity, swelling, tenderness or restriction of movements*. For further details regarding common orthopaedic disorders, refer to Ch 23.

Analysis of general examination: At the end of this session, physical findings must be re-arranged to:

- Correlate with history,
- Identify the system that needs to be focussed in systemic examination,
- Analyse probable differential diagnosis of the disease,
- Assess the severity of the disease process,
- Identify presence of co-pathologies,
- Plan the focus of investigations.

Analysis and interpretation of common physical findings and related information has been discussed in relevant chapters of this book.

CHAPTER

32

Procedures and Equipments

Mukesh Agrawal

Performance of various diagnostic and therapeutic procedures on children is an *art* that can be learned only by practice and experience. This chapter aims to provide the basic knowledge regarding common practical procedures as well as equipments/instruments used for them.

32.1 GENERAL PRINCIPLES

While specific details of various procedures in pediatric practice are discussed in relevant later sections, some general guidelines are as follows:

a. Explain the purpose of procedure to child/parents in simple terms t alleviate their anxiety and ensure cooperation.
b. Obtain written consent for all major procedures. No consent is required for minor procedures, e.g. blood collection, peripheral venous cannulations or day-to-day injections, though the need for the procedure must be explained in advance.
c. Ensure availability of necessary instruments/equipments before the procedure, including proper containers for sending laboratory samples.
d. Ensure adequate pre-procedure sedation and/or vagolytic medications before painful procedures, specially in older children. Local/general anesthesia may be necessary for select procedures.
e. Ensure adequate lighting and environmental temperature at the procedure site. It is preferable to conduct even minor procedures in a separate room rather than in the pediatric ward, to reduce apprehension among other children.
f. Ensure proper restraining of child during procedures, which is essential not only for the success of procedure but also to minimize the risk of injury and complications.
g. Ensure adequate aseptic precautions, including proper hand washing, use of gloves/masks, etc., local antiseptic cleaning/draping of procedure site and use of disposable/sterile equipments.
h. Ensure proper disposal of procedural wastes, e.g. biological fluids, sharps and others, as per waste disposal guidelines of the hospital.
i. Ensure timely collection of reports after diagnostic procedures *or* check the success of therapeutic interventions by suitable investigations, e.g. X-rays.

32.2 INJECTION DEVICES AND ROUTES

An injection may be defined as a *procedure involving piercing of the skin or mucus membrane, either to introduce a substance into the body or to withdraw blood samples, body fluids or body tissues for diagnostic investigations*.

Unsafe injection practices continue to be important health hazards in developing countries including potential risk for transmission of infections. According to an estimate, over 30% of injections in developing countries are considered as unsafe.

An injection is considered unsafe due to: (a) faulty technique, (b) faulty drug/agent given through it, (c) faulty sterilizations of equipments, and (d) faulty waste disposal. This chapter deals with some important issues regarding injections in children, excluding IV injections, discussed elsewhere.

A. Injection devices: Two most important injection devices are syringes and needles.

Syringes may be broadly divided into three types: (a) Glass BD syringes, (b) disposable plastic syringes, and (c) auto-disabled syringes. Glass BD syringes (named after design manufacturer-Becton-Dickinson) are no longer used in routine practice.

- ***Disposable plastic syringes***, available in pre-sterilized (gamma-radiation) pack with different sizes (2-50 ml) , are most widely used syringes at present, for: (a) IM/IV injections, (b) blood sample collections, (c) pleural/ascetic tapping, (d) nasogastric feeding/aspiration/lavage, (e) irrigation of abscess, etc., and (f) infusion of medications by infusion pump.
- ***Single-use autodisabled syringes***, e.g. *uni-ject* or *solo-shot* syringes are preferred choice for immunization

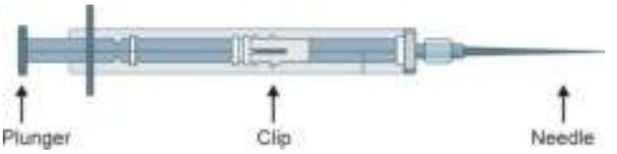

Fig. 32.1: **Autodisabled syringe.**

Fig. 32.2: **Tuberculin syringe.**

purpose and available at many centers under national immunization program. In these syringes, the plunger cannot be withdrawn after single use, to prevent re-use **(Fig. 32.1)**.

- ***Tuberculin or insulin syringe*** is a slender and long one-ml glass syringe with colored plastic or metal piston. While tuberculin syringe is graduated in ml, insulin syringe is graduated in units **(Fig. 32.2)**. Tuberculin syringe is commonly used to administer very minute quantities of drugs for: (a) tuberculin test, (b) BCG vaccination, (c) insulin therapy, (d) test-dose of penicillin, and (e) precise dosing in newborns.

Needles may be broadly divided into two types – *reusable* without any plastic part and *disposable* with plastic shoulder. Reusable syringes are rarely used at present. Disposable needles are pre-sterilized with gamma radiation and available in various thicknesses and lengths, numbered according to the reverse thickness diameter (No. 18 means 1/18 inch thickness). Size 20–26 inch is commonly used in children.

Needles are commonly used for: (a) parenteral drug injections, (b) blood samples collections, (c) withdrawal of drug from vials/ampoules, and (d) addition of drugs into IV lines, apart from, (e) miscellaneous uses, e.g. foreign body removal, etc.

B. Injection routes: Commonly used injections may be broadly divided into four categories: (a) intravenous injections, discussed elsewhere, (b) intramuscular injections, (c) subcutaneous injections, and (d) intradermal injections. Some important aspects of correct injection techniques for various routes of injections **(Fig. 32.3)** are as follows:

- ***Intramuscular injections*** are used for most vaccinations and many parenteral drug administrations. Generally, the *anterolateral aspect of thigh* is the safest and preferred site in infants for IM injections, due to higher risk of underlying nerve injury in gluteal or deltoid injections. Upper and outer quadrant of gluteus maximus may be used for vaccinations beyond infancy.

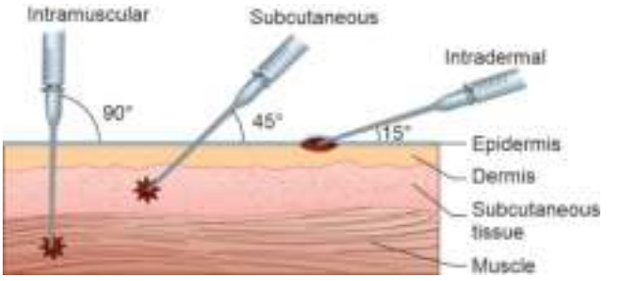

Fig. 32.3: **Correct approach to various types of injections.**

- ***Subcutaneous injections*** are used to administer selected vaccines, e.g. measles, or drugs, e.g. adrenaline. Outer aspect of upper arm is the preferred site for these injections, which should be administered by given by pinching up the skin and subcutaneous tissue with provider's fingers and piercing it at 60° angle, with a subcutaneous needle.
- ***Intradermal injections*** are usually given at shoulder or forearm, for - BCG vaccination, Mantoux testing or penicillin-sensitivity testing. It is essential to stretch the skin over injection site between nondominant thumb and fingers, before piercing it at ~15° with the bevel of needle facing upwards. Only the needle tip should be introduced beneath the skin. A successful intradermal injection is reflected by formation of a wheel at the site.

WHO has launched a ***Safe Injection Global Network*** **(SIGN)** program to encourage use of safe and appropriate injections practices and a WHO steering group has developed standard guidelines for evidence-based best injection practices **(Table 32.1)**.

Important components of these practices include: (a) genuine indication, (b) pre-injection check of product information, e.g. expiry date, etc. (c) pre-injection hand washing, (d) preparation of injection site, (e) use of sterile injection equipments, (f) proper filling/dilution or injection, (g) proper method of injection, and (h) proper waste disposal (Also see Ch 9.8.2).

32.3 VASCULAR ACCESS PROCEDURES

Vascular access procedures are most common parenteral interventions in pediatric wards for therapeutic fluid/drug infusions or diagnostic blood sample collections.

For the sake of description, these procedures may be broadly divided into: (a) peripheral venous cannulations, (b) umbilical vein catheterization, (c) intraosseous cannulations, (d) central venous catheterizations, (e) arterial punctures, and (f) collection of blood samples. The choice of procedure depends on its purpose and available expertise.

A. Peripheral venous cannulation (PVC): Peripheral veins are preferred choice for venous access due to easy

TABLE 32.1: Best infection control practices for intradermal, subcutaneous and intramuscular injections

I. Use sterile injection equipments
- Use sterile syringe and needle for each injection and to reconstitute each unit of medication
- Ideally, use a new, single-use disposable syringe and needle
- Inspect packages for barrier integrity and discard in damaged

II. Prevent contamination of injection equipments and medication
- Prepare each injection in clean designated area, unlikely to be contaminated with blood/body fluids
- Use single-dose vials rather than multi-dose vials
- If multi-dose vial is unavoidable, pierce the septum with sterile needle. Don't leave the needle in stopper for re-use
- Select pop-up ampoules rather than those, which require cutting with a metal file.Protect fingers with a clean barrier, e.g. cotton gauze while cutting the ampoule, if necessary
- Inspect for and discard visibly contaminated medications or those with breached integrity
- Follow product-specific recommendations for use, storage and handling
- Discard a needle, if it has touched any non-sterile surface

III. Prevent needle-stick injuries to the provider
- Anticipate and prevent patient's movements during injection
- Avoid recapping, if necessary, use single-handed scoop technique
- Collect used needles/syringes at the point of use in a puncture-proof sharp's container and seal before it is full

IV. Prevent access to used needles
- Seal sharps' container before transport to designated area for disposal. Don't open, empty, reuse, sell them
- Manage sharps waste in an efficient, safe and environment-friendly way to protect people from voluntary/accidental exposure

V. Other practical issues
- Whenever possible use auto-disable syringes or other devices to prevent needle-stick injury
- Wash/disinfect hands before preparing injection and administering them. Avoid giving injections if hands have local infection/dermatitis. Cover small cuts
- Routine use of gloves are unnecessary. Use single-use gloves if excess bleeding is anticipated
- Routine Swabbing of vial/ampoule tops with antiseptic is unnecessary. If necessary, use a clean single use antiseptic swab with adequate contact time as per product specifications. Don't use stored wet cotton balls
- Routine swabbing of skin before injection is unncecessary but wash visibly dirty/soiled skin. If necessary, use a clean single use antiseptic swab with adequate contact time as per product. Don't use stored wet cotton balls

procedure and less risk of infections/complications than central venous catheterization.

PVC devices: Two most commonly used PVC devices in children are: (a) *over-the-needle catheters* (venflon), and (b) *butterfly or scalp-vein needles*.

- ***Over the needle catheters*** *(venflon)* is the preferred choice for peripheral venous cannulations due to less chances of dislodgement on patient's movements and local thrombophlebitis. These catheters, available as pre-sterilized disposable items in variable sizes (fG 18–24), have two parts: (a) outer teflon or polyurethane sheath (catheter) with connecting port, and (b) inner metallic needle, which acts as stylet during insertion. Apart from PVC, these catheters can also be used for arterial cannulation or as venesection catheter for thin veins **(Fig. 32.4)**. Different sizes of cannula are often color-coded for easy identification, e.g. 20 (pink) 22 (blue), 24 (yellow), 26 (violet).
- ***Scalp vein (Butterfly) needle*** has three parts: (a) a short, fine-bevel metallic needle, (b) a 15–20 cm long polyethylene tube connected to needle with a stopper at other end, and (c) a butterfly-shaped plastic grip at the junction of needle and tube to assist fixation

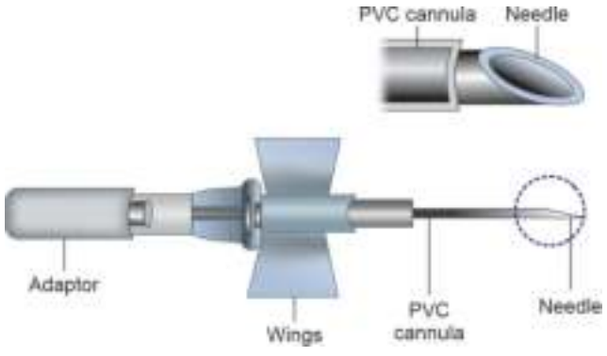

Fig. 32.4: **Over the needle catheter.**

(Fig. 32.5). These needles are available in different sizes (No. 18–24), in pre-sterilized gamma-irradiated pack and should not be re-used.

Scalp vein needles are generally used for: (a) short-term venous cannulation, or (b) blood sample collections in newborns and young children. These needles tend to dislodge easily and should be avoided for prolonged cannulations. Although the name suggests their use for cannulation of scalp veins, these needles may also be used at other sites.

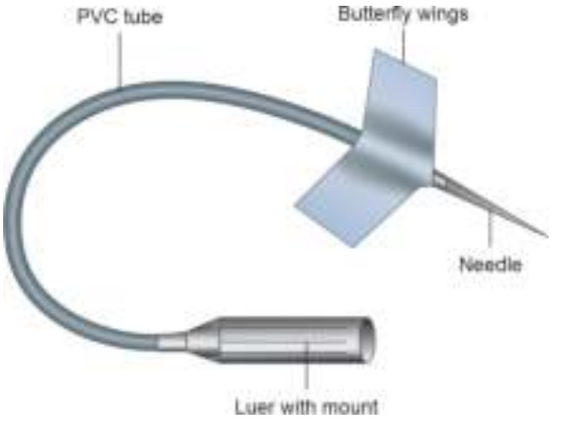

Fig. 32.5: **Scalp vein (butterfly) needle.**

PVC sites: Although the choice of venepuncture site depends on personal preference and experience, a thumb rule is to begin with a vein, which is most prominent, not attempted before and will not interfere with resuscitation efforts or other diagnostic/therapeutic interventions.

Commonly used PVC sites in children are: (a) dorsal veins of hand/foot, (b) great saphenous veins over medial malleolus, (c) cephalic, basilic or median cubital vein over antecubital region, and (d) superficial veins of scalp. Femoral or external jugular venipuncture is rarely used in pediatric practice.

PVC procedure (Venflon): While PVC cannot be learned without actual practice, important steps for *over the needle catheter insertion* are as follows: Select a suitable site > restrain the baby > wash and glove the hands > tie a tourniquet proximal to the site or ask the assistant to compress proximal venous flow > clean the venipuncture site with an antiseptic and allow it to dry for 1–2 minutes–the time required for it bactericidal action > flush the selected catheter/needle with saline to check patency and avoid air-locking > fix the selected vein by stretching overlying skin between two fingers > puncture the skin slightly distal or lateral to intended venipuncture site > advance the needle till blood flows freely > advance the remaining catheter over the needle > withdraw the needle > flush with saline to ensure free forward flow of fluid > fix the catheter with adhesive tape and connect it with infusion set.

Similar steps are used for *butterfly needle* insertion except that it has no overlying catheter and needle itself is left *in situ*.

Complications: (a) local extravasation of fluids due to displaced catheter/needle, (b) local thrombophlebitis, cellulitis or gangrene, (c) distal vasospasm with gangrene, (d) catheter-related bacteremia/septicemia, and (e) air or catheter-fragment embolism. As the risk of catheter - infections rises rapidly after 48–72 hours, even well-placed PVC devices should be changed every 72 hours.

Other sites of peripheral venous access, e.g. Femoral or external jugular venipuncture are rarely used in children due to the risk of concealed hemorrhage/extravasation *or* spasm of neighboring artery.

B. Umbilical vein catheterization is a useful method to obtain venous access in newborns for: (a) IV drug administrations during resuscitation, (b) exchange transfusions, (c) collection of blood samples, and (d) central venous pressure (CVP) monitoring.

Procedure: Umbilical cannulation is possible only in first 5–7 days of life. Although special thin and long umbilical catheters are available, a small diameter infant feeding tube may also be used for this purpose. Important steps in umbilical cannulation are as follows:

Clean the umbilical area with antiseptic and drape it with sterile towels > wash and glove the hands > cut the stump with a sharp scalpel close to its base to visualize three collapsed vessels–single thin-walled umbilical vein and paired thick-walled umbilical arteries > clean the umbilical vein opening with a forceps, if necessary > guide the special umbilical catheter or feeding tube gently into umbilical vein with rotating movements for ~5–15 cm > check the free blood flow into catheter > connect it with infusion set > fix the catheter with purse-string sutures > place a dry gauze over cord area, to prevent contamination.

Complications: (a) local trauma, (b) thromboembolic complications, (c) bacteremia/septicemia, (d) portal vein thrombosis with development of extrahepatic portal hypertension in later life.

C. Intraosseous cannulation: Intraosseous cannulation is a safe, simple and reliable method to administer drugs, fluids or blood products into non-collapsible venous plexus during resuscitation, when IV access is difficult and cannot be achieved within three attempts or 90 seconds. This access is easier to obtain in children < 6 years, though may be attempted even in older cases.

Any IV fluid or drug may be infused via intraosseous route with comparable dose, onset of action and efficacy. However, rapid volume infusions or viscous drugs may need to be administered under pressure to overcome resistance of emissary veins.

Site: The flat anteromedial surface of tibia, ~1–3 cm below the tibial tuberosity is preferred site of intra-osseous cannulation in children <6 years due to large marrow cavity at this site and least risk of injury to adjacent tissues **(Fig. 32.6)**.

Devices: While specific intraosseous needles are available, a regular bone marrow aspiration needle (*Jamshidi type*) is commonly used. Simple wide-bore IV needles or LP needles are not recommended due to chances of blockage and bending.

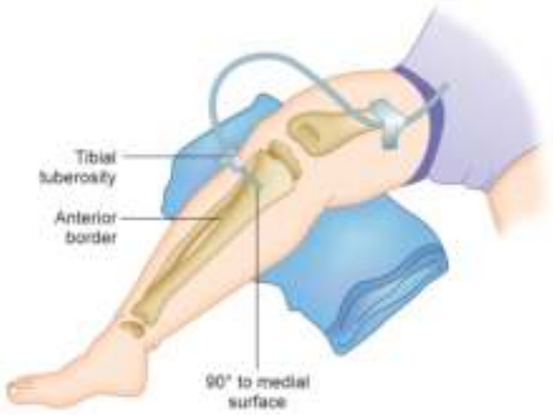

Fig. 32.6: **Intraosseous cannulation.**

Procedure: Important steps in intraosseous cannulation, after proper restraining the child, are as follows:

- Locate and mark the cannulation site by palpation, roughly one finger-width below and medial side of the tibial tuberosity.
- Wash the hands properly and wear gloves.
- Clean the site with an antiseptic and allow it to dry for 1–2 minutes for bactericidal action.
- Check the needle to ensure proper alignment between bevels of outer needle and internal stylet.
- Insert the needle at selected site at 90° to the long axis of bone and advance with a gentle but firm twisting motion till sudden decrease in resistance is felt and needle remains upright without support.
- Unscrew and remove the stylet and check the location by aspiration of bone marrow, if required.
- Flush the needle with 10 ml normal saline to ensure patency and check for any sign of resistance in fluid flow or soft tissue swelling.
- Stabilize the needle with adhesive tape and connect it with infusion set.

Insertion is successful if: (a) the needle remains upright without support, (b) marrow can be aspirated, and (c) fluid flows freely without subcutaneous infiltration.

Complications are rare (<1%) but tends to be more severe than PVC. Hence, this procedure should be reserved only for critically sick children as a temporary measure till other secure venous access is obtained.

Reported complications include: (a) tibial fracture, (b) local skin necrosis or *compartment syndrome*, (c) osteomyelitis and very rarely, (d) fat embolism. Local effects of intraosseous infusions on long term bone growth are negligible.

D. Central venous cannulation (CVC) that reaches up to Superior vena cava or right atrium is used in intensive care for: (a) hemodynamic central venous pressure (CVP) monitoring, (b) frequent blood collections, and (c) prolonged infusion of irritating solutions, e.g. total parenteral nutrition.

A special long silastic or polyethylene catheter is used for CVC, introduced through a large peripheral vein, e.g. subclavian, external jugular or femoral vein by *Seldinger technique.* While details of this procedure are beyond the scope of this book, important steps are as follows: Puncture the vein with a needle > insert a guide wire through the needle into vessel > withdraw the needle, leaving guide wire behind > sheath the catheter over guide wire till superior vena cava under fluoroscopic guidance.

Complications: Although CVC catheters can be kept *in situ* for longer periods than PVCs, risk of complications, e.g. infections, thromboembolism, traumatic bleeding and arrhythmia as well as procedural difficulties are more than PVCs and preclude frequent use in pediatric practice

E. Arterial cannulations Arterial access is required for continuous BP monitoring and collection of arterial blood gas samples or other blood samples in critically sick children. *Arterial lines should never be used for fluid or drug infusions.*

Sites: Radial artery is the preferred site for arterial cannulation, although other peripheral arteries, e.g. brachial, femoral, axillary, dorsalis pedis or posterior tibial arteries may also be used for this purpose. Temporal artery cannulation, though easier, is not advisable due to risk of cerebral thrombo-embolic complications.

Procedure: A heparinized butterfly needle or venflon may be used for temporary arterial puncture for blood sample collections, while special arterial catheters are used for monitoring purpose. The procedure for arterial cannulation is similar to that for venous access, except following considerations:

- Ensure adequacy of collateral flow at selected site, which is vital for local perfusion in the event of arterial spasm during/after the procedure. In case of radial artery cannulation, modified *Allen's test may be used for this purpose*.

  Allens's test: clench the child's hand tightly and raise it above the heart level > occlude both radial and ulnar arteries > lower the arm > open the hand and release pressure on ulnar artery > record the time required for return of color over palm; A reperfusion time of > 6 seconds indicate poor ulnar collaterals and radial puncture on that side should not be attempted.
- Adequate pressure should be maintained for at least 5 minutes over the puncture site after withdrawal of arterial cannula/needle, to prevent oozing from high pressure vessel.

Fig. 32.7: **Heel puncture.**

- A continuous infusion of heparin solution (1 IU/ml saline, 3–5 ml/hour) should be maintained in long-use arterial lines to prevent block and thromboembolic complications.

Complications: Excessive local bleeding and temporary vasospasm with compromised distal perfusion are most important complications of arterial punctures in children, though most cases resolve spontaneously. More serious complications of arterial cannulations, usually seen with indwelling arterial lines include: (a) thrombotic vasoocclusion with distal gangrene, (b) air-/particulate matter-embolism, and (c) systemic infections.

F. Collections of blood samples: Various methods used for collection of blood samples in young children include: (a) peripheral venipuncture with a heparinized scalp vein set, (b) arterial puncture, and (c) *heel-puncture* in newborns and young infants. Radial artery puncture is commonly used to collect arterial blood samples for Blood gas analysis.

Samples may also be collected from existing PVC or arterial lines, though some values, e.g. blood glucose or cultures are unreliable from such samples. Femoral venipunctures, once commonly used, are rarely used at present due to risk of femoral arterial spasm or concealed hemorrhages in femoral space.

Heel puncture is a useful method to collect capillary blood sample in newborns for hematologic, biochemical or blood gas investigations, as follows:

Cover the heel with warm wet towel for 5 minutes to increased local vascularity > clean it with antiseptic > puncture the lateral or medial 1/3rd of heel skin with an stillette, pricked perpendicularly for ~2–2.5 mm depth > wipe off the first drop of blood > collect subsequent flow in capillary tubes **(Fig. 32.7)**.

COMMON TRANSFUSION DEVICES

Apart from the vascular access devices discussed earlier, some other commonly used devices for IV therapy **(Fig. 32.8)** are as follows:

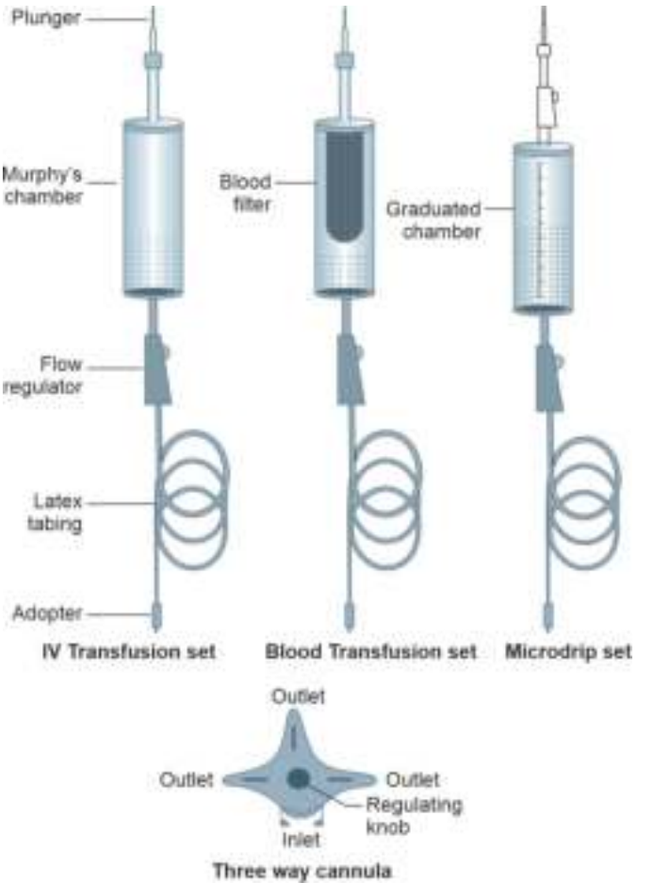

Fig. 32.8: **Transfusion devices.**

a. IV transfusion set is a long PVC tubing 120–150 cm with: (a) IV bottle connector at one end, (b) cannula/needle connector at other end, (c) *murphy's chamber* at 6–12 cm away from bottle end, and (d) flow-rate regulator valve.

Murphy's chamber is used to regulate the flow rate of IV fluid by adjusting the number of drops (16–20 drops/ml) falling per minute. A fluid level must always be maintained in the Murphy's chamber, if necessary after resetting.

b. Blood transfusion set is similar to IV set, except that it contains a filter in Murphy's chamber to filter-out any clots in the infused blood.

c. Microdrip set is also similar to the IV set except that instead of Murphy's chamber, it has a two part PVC chamber. Upper chamber of microdrip set is graduated in ml with a usual capacity 100 ml and drains into lower chamber through a fine metallic needle to reduce the drop size (~60 drops/ml). Microdrip set is used to control accidental infusion of large volumes in very young children and to ensure finer drop-rate control during infusion of potentially hazardous drugs, e.g. dopamine, insulin, etc.

d. Three-way is a small T-shaped glass or PVC device, with two inlets and one outlet. Either of the inlets can be connected to the outlet with the help of a perpendicular knob/screw.

Three-way is commonly used as intermediary connection between Venflon (connected to outlet) and IV tubing (connected to one of the inlet). Third inlet allows: (a) additional IV drug delivery without disconnecting the line, (b) simultaneously CVP monitoring, (c) aspiration of blood samples. Three-way may also be connected during therapeutic throaco-/abdominocentesis to avoid need for repeated disconnections during aspiration and prevent air-entry in the cavity.

32.4 RESUSCITATION PROCEDURES AND DEVICES

Broad concepts of pediatric and neonatal resuscitation (PALS/NALS) have been covered in relevant chapters. This sections deals with common equipments and procedures used in resuscitation.

A. Suction devices may be broadly divided in three categories: (a) central suction system, desirable in intensive care units, (b) portable electric/foot-operated suction machine, commonly used in wards, and (c) oral (*Delee's*) mucus extractor. Important considerations during suction are:

- Suction catheter must be sterile/disposable, flexible and non-traumatic. A plain rubber catheter is preferred *except* to remove thick secretions or particulate matter by rigid catheter, e.g. nasogastric tube.
- Optimum suction force should not exceed ~80–120 mm Hg (~30 in newborns) to avoid mucosal trauma.
- Suction time at one attempt should not exceed 5 seconds to avoid prolonged hypoxia. If necessary, O_2 supplement is necessary before next attempt.
- Heart rate should be monitored to detect significant bradycardia, due to vagal stimulation.

Important complications of suction procedure are: (a) mucosal trauma, (b) nosocomial infection and rarely, (c) sudden cardiorespiratory arrest due to vagal stimulation.

Delee's mucus extractor is a small, disposable, PVC suction device for neonatal resuscitation, with three parts: (a) central bulb to retain aspirated mucus, connected to, (b) a patient's end tube, and (c) a resuscitator's end tube with adopter **(Fig. 32.9)**. As the resuscitator sucks from his/her end of tube, patient's mucus is collected in the bulb by negative pressure. *Advantages:* Delee's mucus extractor is the preferred suction device for intranatal or immediate postnatal resuscitation due to: (a) simple to use, (b) non-expensive, (c) disposable, (d) does not require electricity.

However, It is not effective beyond neonatal period, due to limited negative pressure, created by resuscitator's suction (<50–60 mm Hg).

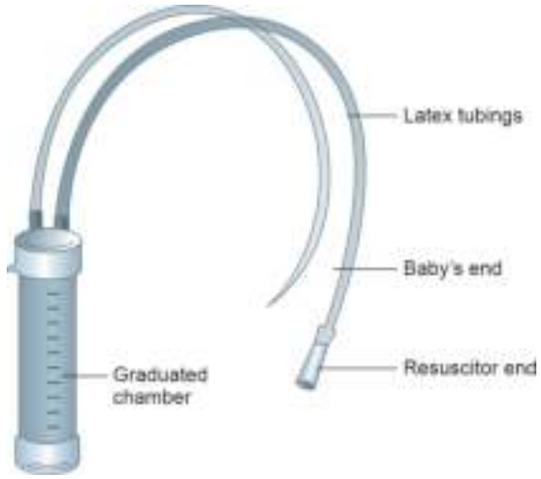

Fig. 32.9: Delee's mucus extractor.

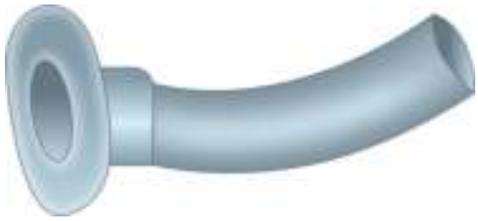

Fig. 32.10: Oropharyngeal airway.

B. Oropharyngeal airway is a curved plastic/metal device of variable size **(Fig. 32.10)**, used to prevent glossoptosis and provide clear airway/suction channel in unconscious children.

Appropriate size may be estimated by placing its flange at the corner of mouth, when the tip should reach the angle of mandible. It should not be used in a conscious/convulsing child to prevent tongue bite, due to risk of further trauma.

C. Oxygen delivery devices: Oxygen therapy aims to raise O_2 content in inspired air (FiO_2) in order to support blood oxygenation in hypoxic states and maintain PaO_2 >60–70 mm Hg or SaO_2 >95%. Common oxygen delivery devices may be broadly divided into three categories: (a) *low-flow devices*, e.g. direct nasal catheters/prongs or face-masks, (b) *high-flow devices* face-tents or oxygen-hoods, and (c) *directed flow devices*, e.g. bag/mask ventilation or endotracheal tube. Efficacy of these devices varies with O_2 flow rate and mixing with expired/environmental air **(Table 32.2)**. Some commonly used oxygen delivery devices are as follows **(Fig. 32.11)**:

Nasal cannula is a simple low-flow oxygen delivery device, with two short plastic prongs fixed to a hollow face-piece. These prongs are inserted in anterior nares and O_2 is delivered into nasopharynx. Though simple to use, nasal cannula is suitable only for children with

TABLE 32.2: Common oxygen delivery devices

Device	*Flow (L/min)*	*FiO_2*
Cannula/catheter	2–4	20–40%
Simple mask	4–6	30–40%*
Venturi mask	6–10	40–60%
Face tent	10–12	~40%
O2 hood/tent	10–12	~80%*
Bag-mask	Adjustable	100%

*up to 60–70%, if tight-mask and reservoir is used

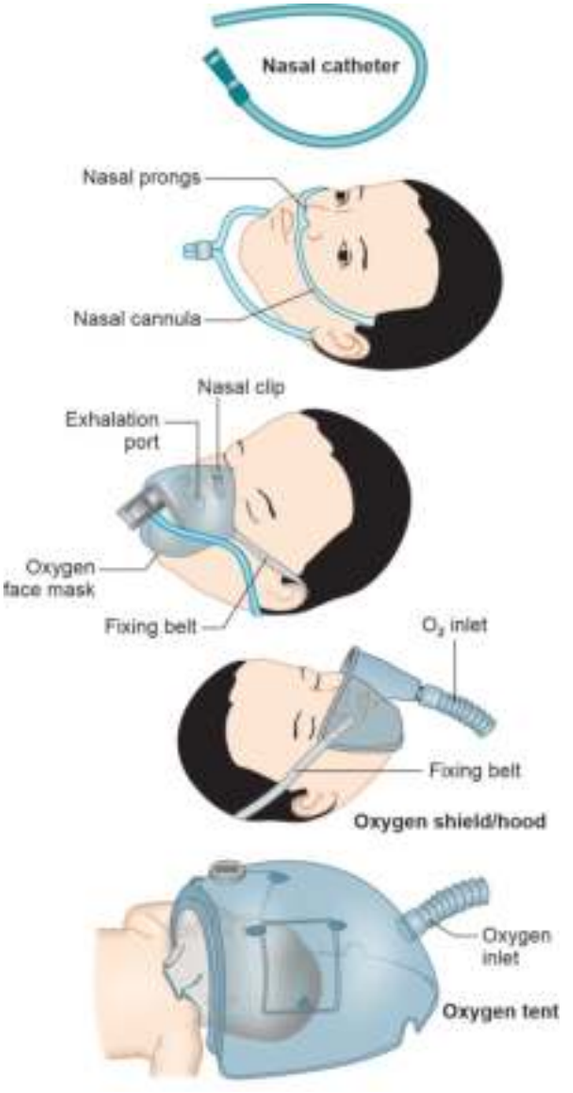

Fig. 32.11: Oxygen delivery devices.

minimum oxygen requirements due to: (a) limited FiO_2 delivery, i.e. 20–40% at flow-rate of ~4 L/min, and (b) variations due to nasal/oropharyngeal resistance and tidal volume. Oxygen flow-rates of >4 L/min irritate nasopharynx without much improvement in oxygenation.

Nasal catheter is a simple rubber catheter with multiple holes in distal 2 cm, which is lubricated and inserted into one nostril till it reaches nasopharynx. It has no advantage over nasal cannula with two major disadvantages: (a) local nasal trauma, and (b) gastric distension, if inadvertently placed in esophagus.

Face-mask consists of three parts: (i) rubber/PVC body, (ii) standard 15/22 mm connecting port, and (iii) face-seal. Two types of face-masks are available-*round-rim* face-seal and *anatomical-shape* face-seal. An ideal mask should be: (a) transparent to allow monitoring for cyanosis and vomiting, (b) non-traumatic with cushioned face-rim, (c) anatomically fitting to allow good air-seal, and (d) proper size to cover the nose and mouth but not the eyes.

A minimum flow-rate of 6 L/min should be used with face-masks to prevent re-breathing of expired CO_2. A face mask delivers ~ 35–60% FiO_2 at oxygen flow rate of 6–10 L/min. Many modifications, e.g. *partial re-breathing mask*, *non-rebreathing masks* and *venturi-type masks* are also used to deliver higher FiO_2.

Uses: Apart from: (a) oxygen delivery, face masks are also used for, (b) bag and mask ventilation in emergency resuscitation, (c) aerosol therapy in young asthmatics via nebulizer or spacer/MDI.

Sterilization: Although pre-sterilized disposable masks are preferable, re-usable masks may be used after running-water wash, chemical sterilization and drying.

Oxygen hood/tents are high-flow clear plastic shells that cover face (*face tent/shield*), head (*oxygen hood*) or upper part of body (*oxygen tent*), which deliver ~40–50% of FiO_2 at the oxygen flow rate of 10–15 L/min. Although ~80–90% FiO_2 may be delivered via well-fitted oxygen hood, these hoods are usually not enough for use in children beyond infancy.

D. Bag and mask ventilation is the simplest method for assisted ventilation in a child with inadequate ventilator efforts.

Indications: (a) intermittent positive pressure ventilation (IPPV) by face-mask or endotracheal tube, (b) continuous positive airway pressure ventilation or CPAP (connected with PEEP valve to maintain end-expiratory pressure of ~5–10 cm H_2O).

Resuscitation bag: Although many types of resuscitation bags are available, most commonly used ***is*** *AMBU bag* (***A***mbulatory ***M***anual ***B***reathing ***U***nit).

A resuscitation bag has following parts: (a) *patient outlet*, to which face mask is connected, (b) *one-way fish valve* to allow escape of expiratory air, (c) *pressure-limited pop-off valve* set at 35–45 cm H_2O to prevent barotrauma, (d) *self-inflating rubber bag* of variable sizes (250–750 ml), (e) *wide air-inlet* on other end that may also be connected with oxygen reservoir, and (f) *narrow oxygen inlet* to connect with O_2 source **(Fig. 32.12)**.

Fig. 32.12: **Resuscitation bag.**

A self-inflating bag, not connected to oxygen source, delivers room air (~21% O_2), while ~30–40% oxygen may be delivered after connecting it with oxygen inflow of 10 L/minutes. For higher oxygen concentrations (~90%), the air inlet should be connected with ***Oxygen reservoir*** or *rebreathing-reservoir* - a small bag or corrugated latex tube with open ends. In this setting, some oxygen in resuscitation bag enters the reservoir during each compression to enrich gaseous mixture for next breath.

Complications: (a) barotraumas, e.g. pneumothorax, due to use of excessive pressure, (b) gastric distension, when used with face mask or misplaced endotracheal tube. Gastric distension may be minimized by inserting a nasogastric tube or ***Sellick maneuver*** (pressure on cricoid cartilage to occlude proximal esophagus).

Contraindications: Bag and mask ventilation is contraindicated in newborns with: (a) kerosene poisoning to avoid risk of aspiration, and (b) diaphragmatic hernia (intestinal distension may accentuate respiratory compromise). However, they may be ventilated manually with resuscitation bag through endotracheal tube.

Self-inflating bags with fish-mouth valve should not be used to provide supplement oxygen in babies with spontaneous efforts, as many of them cannot generate enough inspiratory efforts to open the valve.

E. Endotracheal intubation is the most effective method to ensure adequate airway and deliver 100% FiO_2 via assisted manual or mechanical ventilation.

Indications: (a) Persistent airway obstruction, (b) poor response to bag-mask ventilation, (c) assisted mechanical ventilation during resuscitation, (d) endotracheal aspiration of mucus, meconium or foreign liquids, e.g. milk, (e) general inhalation anesthesia, (f) intratracheal instillation of drugs, e.g. surfactant in hyaline membrane disease or adrenaline during resuscitation.

Equipments required for ET intubation include laryngoscope and Endotracheal tubes **(Fig. 32.13)**.

- **Laryngoscope** is a metallic equipment with two parts a *handle* with batteries and a *blade* with light source. Two types of blades are available - straight blade (*Miller type*) or curved blade (*Macintosh type*). Though the choice depends on personal experience, generally straight blade is preferred in infants and children <8 years due to relative anterior and cephalad location of larynx.

  Both blades are available in four sizes (0–3)—*Size 0 for preterms/low birth weights, 1 for neonates and infants, 2 for 2–10 years age-group and 3 for older cases*. Post-use, laryngoscope should be cleaned by thorough washing under running water, followed by chemical sterilization or autoclaving.

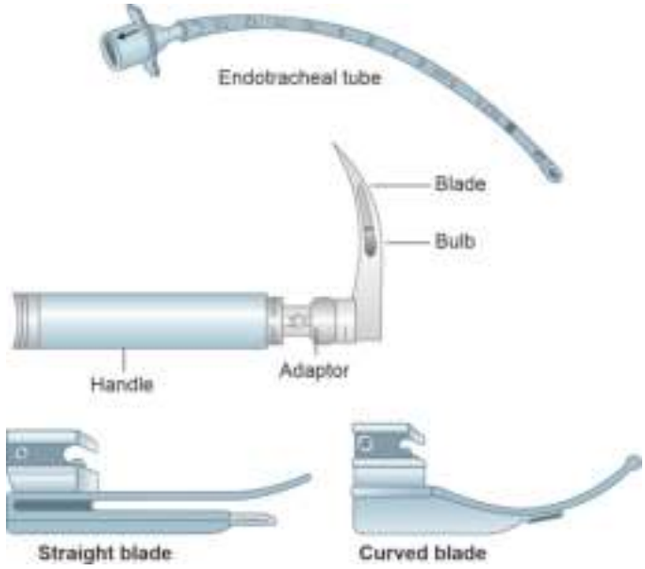

Fig. 32.13: **Laryngoscope, blades and endotracheal tube.**

- **Endotracheal (ET) tube** is a disposable, translucent *portex* tube, which may be *plain* or *cuffed* in the center. Cuffed tubes are self-retaining when inflated with air (not with water due to risk of aspiration) but rarely used in young children, as normal anatomically-narrow cricoid cartilage in them itself provides a functional cuff. ET tubes are pre-sterilized by gamma radiation and disposable.

  ET tubes are available in various sizes or numbers, denoting internal diameter (2–16 mm). Generally 2.0–2.5 size is required in preterms, 3.0–3.5 in full-terms and 4.0–4.5 in infants. Beyond infancy, the required size may be calculated as ***age in years/4 + 4***. As a thumb rule diameter of the ET tube should be equal to the diameter of patient's little finger.

  Most ET tubes have a *longitudinal radio-opaque line* for X-ray confirmation of location and a *transverse black line* proximal to the tip, termed as *vocal cord guide*. Vocal cord guide should be at the level of vocal cords to ensure that the tip of the tube is above the bifurcation of trachea.

Procedure: Although ET intubation is an art, learned only by practice, important steps include:

Check the proper functioning of laryngoscope and select proper size of ET tube, > place the patient on a flat surface with head end near the edge, > position the head

with neck in semi-extended position to ensure proper alignment between mouth, pharynx and trachea > hold the laryngoscope with left hand and insert the blade into mouth in midline till it reaches the base of tongue and epiglottis is visualized > insert the endotracheal tube into glottic opening under laryngoscopic guidance > advance it till mid-trachea* > ensure the correct position**.

* Desired depth of ET insertion is calculated as - ***Age in years/2 + 12*** in cm from alveolar margins).

** Position and patency of ET tube must be checked after insertion by: (a) observation of bilateral chest movements, (b) auscultation for bilateral air entry into chest, (c) auscultation for absent breath sounds over stomach, (d) check X-rays and (e) recording $ETCO_2$ levels, if possible.

Complications of ET intubation include: (a) local trauma, (b) sudden laryngospasm during attempted insertion, (c) hypoxia during intubation procedure*, (d) subsequent tube-block by secretions**, (e) unilateral lung collapse/emphysema due to misplaced tube, and (f) nosocomial infection. ET intubation for prolonged period may cause—(a) dependence/difficult weaning, and (b) late tracheal stenosis.

*IPPV with 100% oxygen via bag/mask should be given before and between the attempts of intubation, to prevent prolonged hypoxia. Each intubation attempt should not last for >30 seconds, before next IPPV. During procedure, baby should be monitored for bradycardia and color (cyanosis/pallor) to detect severe hypoxia.
**_Post-intubation_, position and patency of tube should be checked periodically by abovementioned methods and repeated suction is frequently required to maintain tubal patency.

F. Tracheostomy is indicated in children with airway obstruction or difficult intubations, using a disposable ***tracheostomy tube*** **(Fig. 32.14)**. It serves the same purpose as intubation, with an advantage of reducing dead space, but disadvantages of increasing the risk of infection, tracheal injury and sub-glottic stenosis. Procedural details of tracheostomy are beyond the scope of this book.

Fig. 32.14: Tracheostomy tube.

32.5 AEROSOL DEVICES AND TECHNIQUES

Aerosol therapy has revolutionized the management of asthma. ***Aerosol*** is a suspension of the drug in gaseous medium, which is directly deposited in lower airways on inhalation via special devices. For the drug *to reach* lower airways, aerosol particle size should be <5 µ. An external propellant or deep inspiration is used to deliver the gas at desired site.

Although only 10–15% of inhaled drug reaches the lower airway by these devices, major benefits accrue from the fact that the drug is directly delivered at the site of action with: (a) rapid onset of action, and (b) minimum side effects due to miniscule doses.

Various types of aerosol devices include: (a) metered dose inhaler (MDI) with/without spacers, (b) dry powder inhalers (DPI), and (c) nebulizers, each with own advantages and disadvantages **(Table 32.3)**. The choice of device depends on the patient's age, cooperation and feasibility.

Generally, nebulizers are preferred in acutely sick hospitalized children. For domiciliary use, direct MDI is preferable in children >6 years, DPI for children between 3–6 years and MDI with spacer/mask in those <3 years of age.

Currently, almost all β-agonists and steroids preparations are available as aerosols (Ch 16.8). Some commonly used aerosol devices are discussed as follows:

Metered dose inhaler (MDI) is a *pressure-actuated* aerosol device that delivers pre-fixed dose of aerosol particles (3–6 µ) during each actuation, forced out by a liquid propellant at the velocity of ~100 km/hour. Released drug may be inhaled directly or via a spacer with/without facemask. With MDI, ~10% of inhaled drug reaches the target airways.

Device: MDI consists of two separable parts: (a) pressurized aluminum canister with a valve and atomizing needle, which fits into, (b) outer plastic actuator sleeve with mouth piece **(Fig. 32.15)**. The valve allows only a measured quantity of drug to be released after each accentuation.

TABLE 32.3: Comparison of various aerosol devices

	Nebulizer	*MDI*	*DPI*
Ease of use	Poor	Easy	Easy
Portability	Poor	Simple	Simple
Cost	High	Less	Least
Time needed	10-15 min	1-2 min	1-2 min
Coordination	Nil	Needed	Nil
Maintenance	Servicing	Nil	Minimal
Drug mixing	Possible	Available*	NA**

*Combination MDI available. **Combination DPI not available.

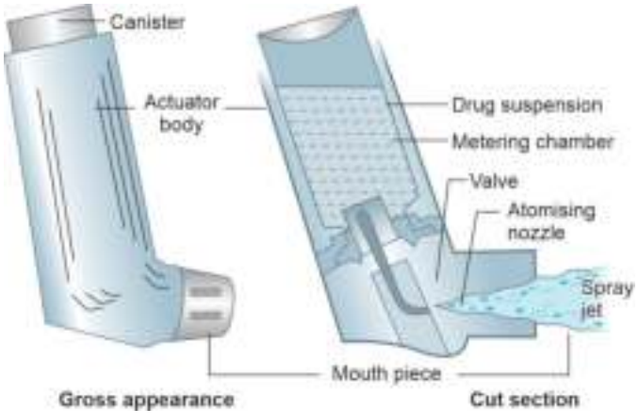

Fig. 32.15: **Metered dose inhaler.**

Pressurised canister contains: (a) *active drug* preparation, (b) *propellant*, e.g. CFC, (c) *surfactants*, e.g. Sorbitan trioleate, oleic acid or lecithin, to prevent clumping of drug particles, and (d) *preservatives*, e.g. Benzalkonium chloride or metabisulfite.

Procedure: Adequate drug delivery via MDI requires proper coordination between drug release and inspiration, which can be acquired only by proper training and practice. Important steps include: shake the inhaler thoroughly > uncap mouth piece > hold the inhaler upright > exhale after tidal breathing > place the mouth piece in mouth and seal it with lips > press (actuate) the canister with simultaneous intake of a *slow-deep breath* > hold the breath for 5–10 seconds > breath out after removing inhaler.

After inhalation of steroid-aerosols, mouth must be rinsed with water to avoid local drug deposition and secondary oral candidiasis.

Cleaning: Outer plastic casing should be cleaned at least once a week by-remove the inner canister > immerse plastic body in warm water > rinse it under running water > dry > replace canister. Drug canister should not be immersed or rinsed.

Advantages: (a) self administration, (b) small and portable, (c) independent of inspiratory airflow.

Disadvantages: (a) need for synchronized actuation and inhalation*, (b) *cold-freon* effect, (c) high drug deposition in the oropharynx (80% of inhaled drug), (d) adverse environmental effect with ozone depletion by CFC-containing canisters. However, most of the currently available MDIs are CFC-free.

*Consequent to the need for synchronized actuation-inhalation-breath holding, direct MDI is unsuitable for children <6 years or during acute severe asthmatic attack. In these cases, it may be used along with a *spacer,* discussed below.

Spacers are devices, which hold the medication for a few seconds after it is released from the MDI, thus obviating the need for actuation-inhalation-breath holding synchronization. With MDI-spacer combination ~15% drug can reach target airways.

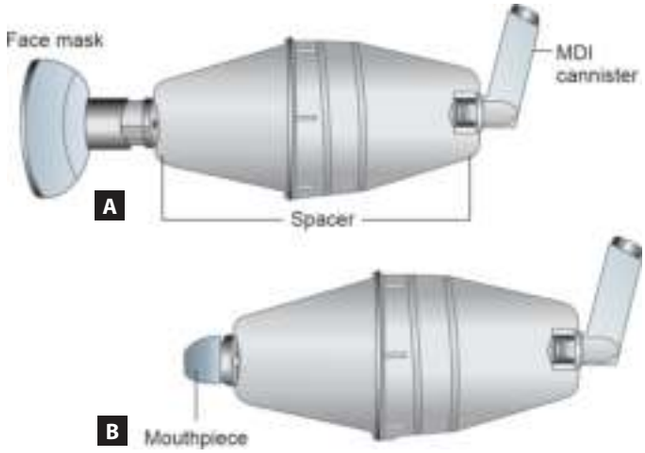

Fig. 32.16A and B: **Spacer: (A) with face mask; (B) without face mask.**

Device: Spacer devices have a two-piece compartment with combined volume of 250–820 ml, made up of antistatic polycarbonate/polyamide material, with one inlet for MDI canister and another outlet as mouth-piece **(Fig. 32.16)**. After actuation of MDI device, adequate quantity of aerosol remains in the spacer for ~10–40 seconds, during which it may be inhaled by multiple inspiratory efforts either directly through mouth-piece or via a face-mask (in infants). Some spacers also have a one-way valve that opens only during inspiration.

Procedure: Assemble the spacer > fix the MDI canister on inlet > close the lips around mouth-piece to create a good seal > actuate the canister > inhale deeply through mouth and hold the breath as long as possible > young children may have to breathe 5–6 times > repeat the second dose after at least 1 minutes, if necessary. A proper-size face-mask may be used to facilitate administration in children <3 years.

Cleaning: Spacer should be cleaned at least twice a week by - separate two halves > rinse in warm water > wipe dry with soft-cloth.

Advantage: MDI spacer with face-mask is ideal choice for day-to day aerosol therapy in children <3 years due to: (a) no need for actuation-inhalation synchronization, (b) least drug deposition into oropharynx (~10% of inhaled drug, reducing local steroid side-effects, (c) increased drug delivery to the lungs, (d) no cold-Freon effect, (e) multiple dose administration at one sitting.

Dry powder inhalers (DPI) are breath-actuated devices, which use the patient's own inspiratory force to deliver the drug powder into lungs, using a special device-*Rotahalers, Dischalers, Turbohaler, Spinhaler*, etc. No propellant is used in them.

Device: Commonly used *Rotahaler* is a two-part transparent chamber with upper half having a mouth-piece and a square hole to insert the medicine capsule, i.e. Rotacap. Lower half (base) has a fin to break the

Fig. 32.17: **Dry powder inhaler.**

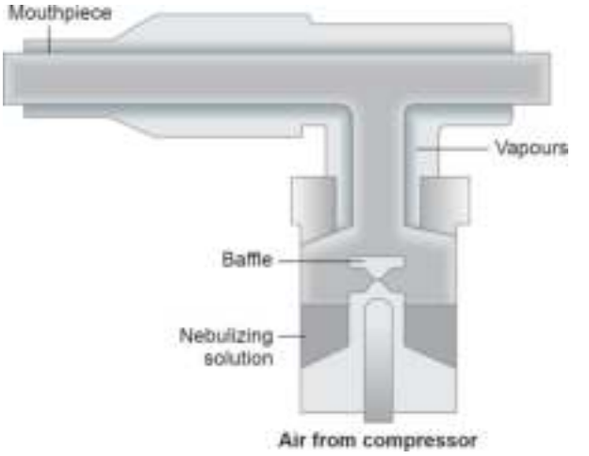

Fig. 32.18: **Hudson chamber for nebulization (Schematic representation).**

capsule inchamber, when it is rotated against the upper half **(Fig. 32.17)**. Drugs for use with rotahalers are available as dry powders, tagged with an inert carrier, e.g. lactose and packed in a gelatin capsule.

Procedure: Assemble the rotahaler > insert a rotacap in square hole (transparent end first) > rotate the base to break the capsule and release drug powder into the chamber > breathe-out fully > seal the mouthpiece with lips > inhale as rapidly* as possible > remove the rotahaler and hold the breath as long as possible. Sometimes 2–3 additional inhalations are necessary to finish the powder.

* Note that very rapid inhalation is must with DPI use, while MDI should be inhaled deeply and slowly.

Cleaning: Rotahalers should be cleaned at least twice a week as follows–separate two halves > remove empty capsule > rinse with running water > dry > reassemble.

Advantages: DPI is the ideal choice for day to day aerosol therapy in children between 3–6 years, due to (a) no need for actuation-inhalation coordination, (b) easy to assemble, use and carry, (c) economical than MDI, and (d) environment friendly (CFC free), and (e) multiple aerosol drugs can be administered with same rotahaler.

Disadvantages: Major limitation of DPI is the need for good inspiratory effort as a driving force, which may not be possible during severe acute attack*. Despite best efforts with DPI, only ~5% of inhaled drug reaches the target airways and lungs. Further, the capsules have to be carried separately and may become sticky and less dispersible in humid conditions or prolonged storage.

*Children unable to use DPI during acute attack, may be switched on MDI with spacer.

32 Nebulizer

Nebulizer is an electric-device, used to convert a liquid drug into fine mist that can than be inhaled easily. Based on the methods of aerosolization, nebulizers may be divided in—(a) jet nebulizer, and (b) ultrasonic nebulizer.

Device: Commonly used Jet nebulizers use a compressed air/oxygen flow (4–6 L/minute) to convert the liquid drug into mist with a particle size of 2–5 μ. Drugs, available as special nebulizing solutions, are filled into a special *Hudson's chamber* that has a baffle against the air/oxygen inlet to create necessary turbulence for mist formation **(Fig. 32.18)**. This mist can be inhaled via a face-mask.

Procedure: Fill the desired dose of nebulizing solution in Hudson chamber > add normal saline* to make-up a volume of 2–4 ml > fix a face-mask over chamber-outlet > start the machine to check adequate mist formation > fix the face mask over patient's face covering mouth as well as nose properly > allow tidal inhalation till the chamber is empty.

Note that only normal saline, and *not* the distilled water, should be used as diluent in Hudson chamber, as hypo-osmolar distilled water mixture may provoke reflex bronchospasm. However, presently readymade liquid nebulizing formulations are available for use..

Cleaning: Hudson chamber, tubings, mouth-piece and mask should be cleaned with running water after each use. After each day, immerse all these components in warm water/mild detergent for 2–3 minutes > scrub well > immerse in a disinfectant, e.g. acetic acid for 10 minutes > rinse under running water > dry in air.

Advantage: Nebulization is the preferred choice for aerosol therapy during acute severe asthmatic attack, due to: (a) no need for deep or rapid inhalations, (b) multiple drugs, e.g. β-agonists and steroids may be mixed and inhaled together, (c) continuous therapy with higher doses is possible, (d) no reflex-cough, as sometimes seen with MDI/DPI.

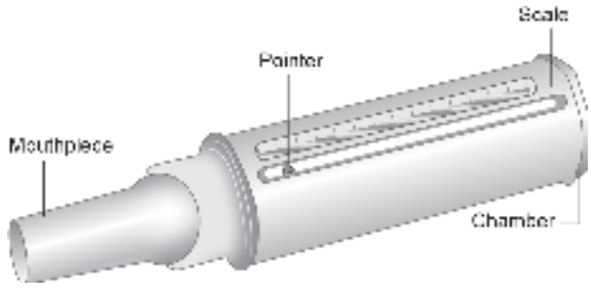

Fig. 32.19: **Peak flow meter.**

Disadvantage: (a) Expensive and needs regular electric supply, (b) bulky equipment, difficult to carry, (c) risk of air-borne infections if not cleaned properly or Hudson chamber is reused for many patients.

Peak expiratory flow meter is a simple and portable equipment to record *PEFR*-a reliable indicator of the severity of airway obstruction in asthma.

Components: Commonly used *Mini-Wright's peak flow meter* is a 20–25 cm long plastic tube with three parts: (a) detachable mouthpiece, (b) main body with a graduated scale (Lt/min) to read PEFR, and (c) diaphragm inside the tube attached to an external pointer that moves on main body's scale **(Fig. 32.19)**.

Uses: PEFR measurements are used for: (a) assessment of the severity of acute attack and response to therapy, and (b) long-term monitoring of the course of disease.

Procedure: Move the pointer to zero > hold the peak flow meter horizontally > ask the patient to breath-in as deep as possible > place the mouthpiece in patient's mouth, sealing it with lips > ask him/her to blow-out as hard and fast as possible > record the forward displacement of pointer on the scale that gives direct value of PEFR in liters/minutes.

As it is an effort-dependent parameter, minimum three reading should be recorded before taking the *best record as patient's PEFR*.

32.6 ASPIRATION AND BIOPSY PROCEDURES

This sub-chapter deals with some common diagnostic or therapeutic aspiration/biopsy procedures in children.

Lumbar puncture (LP) is a common procedure for the diagnosis and treatment of various neurological disorders.

Indications:

- Diagnostic CSF examination for:
  - Meningitis, encephalitis, subarachnoid hemorrhage
  - D/d acute poliomyelitis vs. Guillain-Barre syndrome
  - CNS involvement in septicemia, leukemia, etc.
- Therapeutic CSF drainage in raised ICP,
- Intrathecal drug administrations, e.g. methotrexate, tetanus immunoglobulins, etc.,

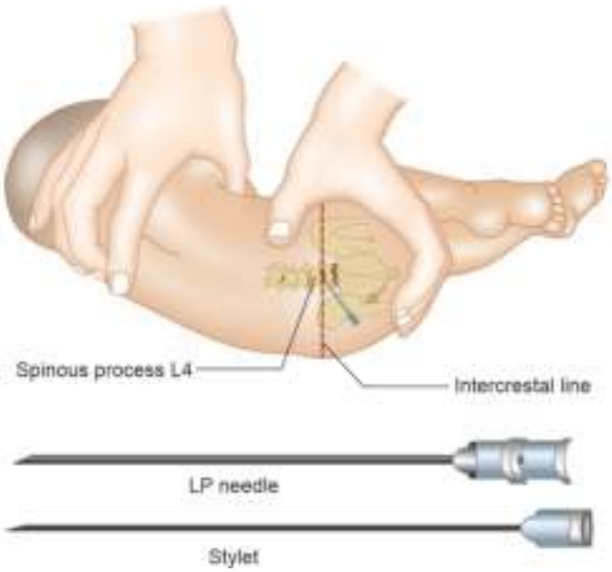

Fig. 32.20: **Lumbar puncture.**

- Intrathecal contrast injections during myelography, CT scan, etc.
- Spinal anesthesia.

Contraindications:

- Raised ICP with papilledema*, due to risk of sudden brain coning/herniation,
- Local skin infection over the LP site, and
- Abnormal coagulation profile or thrombocytopenia <20,000/mm^3.

*If unavoidable, a guarded LP with attached manometer may be performed after mannitol infusion in these cases.

Prerequisites: (a) informed written consent, (b) fundus examination, to exclude papilledema.

Instrument (LP needle): LP needle is a stainless steel needle with two major parts: (a) main *hollow needle* with beveled end, relatively malleable body and thick grooved/notched base, and (b) *inner stiletto* with a small knob that fits into groove of main needle **(Fig. 32.20)**. Although available in various sizes (No. 18–24), only no. 23 and 24 LP needles are used in children. A disposable IV needle (G 20–21) may also be used in children instead of specific LP needles, if required.

Uses: (a) lumbar puncture, (b) ventricular or cisternal puncture, (c) pericardial, pleural or peritoneal tapping, (e) fine needle aspiration cytology (FNAC).

Sterilization: *Autoclaving*, though disposable LP needles are also available.

LP Site: Inter-vertebral space between L 4–5 or 3–4, in midline.

Procedure: Lateral decubitus position with maximally flexed spine is preferred, though sitting position may be used in some cases. Important steps include:

Restrain and position the child > clean the site with an antiseptic > drape the surrounding area > palpate the

desired space, > insert the needle (with stylet, if LP needle is used) slowly, in midline directed 10–15 cephalad, till sudden loss of dural resistance > look for CSF outflow after removing the stylet > collect 2 ml of CSF > withdraw the needle > seal with tincture benzoin. Patient should be kept in head-low position for few hours.

Complications are rare after LP except:

- Post-procedure headache for 6–8 hours
- Sudden death due to coning of brain-stem in cases with raised ICP,
- Iatrogenic meningitis (exogenous infection), and
- Local inclusion dermoid after many years.

Note that:

- A ***dry tap*** indicates faulty technique or subarachnoid block. In such case, procedure should be repeated in a higher intervertebral space.
- A ***hemorrhagic tap*** may be due to local trauma or sub-arachnoid hemorrhage. Traumatic CSF is more bloody in the beginning and clears gradually (*Three-test tube test*).

Subdural tap is indicated for etiological *diagnosis* or *therapeutic* drainage in subdural effusions, empyema or hematoma in children with open anterior fontanel.

Procedure: A disposable 21 G IV needle or LP needle is used for this purpose, with following steps:

Shave the scalp > restrain the child > clean the scalp with antiseptic and drape it > palpate anterior fontanel and mark its lateral angles > slowly introduce the needle at one of the lateral most angle perpendicular to the scalp **(Fig. 32.21)**, till a feel of *give-away* is obtained as dura is pierced and subdural fluid starts flowing > collect the sample *without aspiration by a syringe* > withdraw the needle > apply firm pressure over the site for 2–3 minutes and seal the site > repeat the procedure on other side with a separate needle, even if first tap is dry.

Complications: (a) transient CSF leak, (b) hemorrhage, (c) infection, and (d) porencephaly, if brain tissue was punctured.

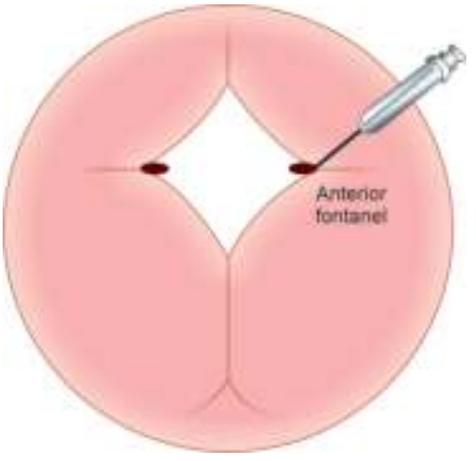

Fig. 32.21: **Site for subdural or ventricular tap.**

Ventricular tap is usually indicated to collect CSF sample for diagnosis/exclusion of ventriculitis in: (a) non-resolving meningitis, (b) before VP shunt in hydrocephalus. Shunt block is likely in presence of ventriculitis with high CSF protein/cell content.

Procedure is similar to subdural tapping, except that—(a) longer needle is used due to greater depth of ventricles, and (b) needle is directed towards the inner canthus of ipsilateral eye rather than at 90°.

Bone marrow aspiration is commonly used to obtain marrow sample for diagnostic/therapeutic purpose. An alternative method – *Trephine biopsy* may be required in cases with dry bone marrow aspiration.

Indications: Diagnostic bone marrow aspiration is indicated in suspected:

- Aplastic anemia.
- Leukemia or other malignancies (for staging).
- Chronic refractory anemia, e.g. megaloblastic anemia.
- Hemo-parasitic infestations, e.g. malaria/kala-azar.
- *Chronic* immune thrombocytopenic purpura.
- Primary marrow disease, e.g. myelofibrosis.
- Metabolic storage disorders, e.g. Gaucher disease.

Repeated aspiration is necessary in many cases to assess the therapeutic response.

Contraindications: (a) severe bleeding tendency, (b) local infection, e.g. osteomyelitis (use other sites).

Instrument (bone marrow aspiration needle): Bone marrow aspiration needle is a short (4–6 cm), thick, stout, non-flexible, stainless steel needle with three important parts: (a) main needle, (b) *trochar* with a knob on external end, and (c) adjustable *guard* **(Fig. 32.22)**. The guard prevents accidental excess penetration of the bone and deeper tissue injuries during insertion.

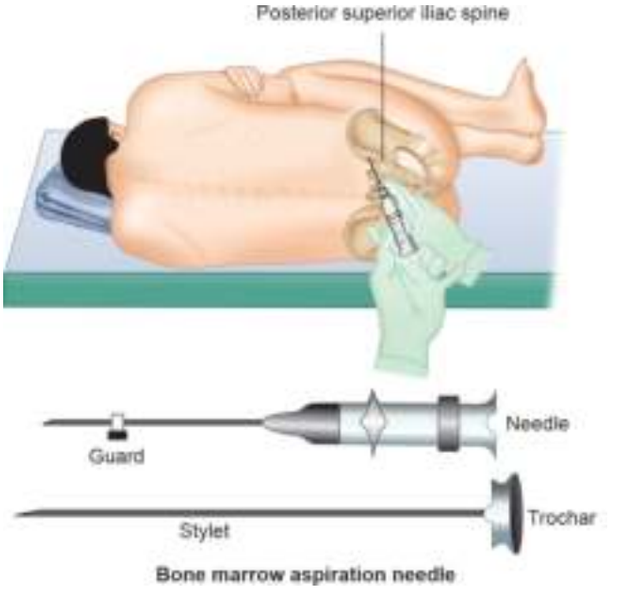

Fig. 32.22: **Bone marrow aspiration.**

Uses: (a) diagnostic marrow aspiration, (b) intraosseous cannulation for emergency fluid/drug therapy, and (c) bone marrow transplant.

Pre-requisites: (a) informed consent, (b) normal coagulation profile and platelet count.

Sites: The choice of bone marrow aspiration site depends on the patient's age as follows:

a. Tibial tuberosity in children <2 years,
b. Anterior superior iliac spine *or* iliac crest in older children and
c. Mid-manubrium sternii (sternal puncture), if other two options are not possible.

Procedure for marrow aspiration include:

Clean the selected site with antiseptic > drape the surrounding area > local anesthesia with 2% xylocaine, though not necessary in very young children, > adjust the guard at nearly 1.5 cm from the tip, > palpate the precise site > insert the needle (with stylet) with boring action, till resistance is felt > remove the stylet > connect a syringe and aspirate 0.5–1.0 ml of bone marrow > withdraw the needle > seal the site with Tinc. benzoin > prepare smears.

Complications: While local pain and tenderness is inevitable for 24–48 hours, important complications include: (a) local bleeding and hematoma, (b) trauma to deeper structures, and (c) infection, e.g. osteomyelitis.

Dry tap indicates: (a) faulty technique, (b) severely aplastic bone marrow, (c) primary marrow disease, e.g. myelofibrosis or myelosclerosis, or (d) severe marrow infiltration, e.g. in malignancies. *Trephine biopsy,* using *Jamshidi-Swain needle* is indicated in these cases.

Liver biopsy is commonly used for histological diagnosis and/or follow-up of primary or secondary liver disorders.

Indications: Diagnostic liver biopsy is indicated in:

- Chronic liver disease or cirrhosis.
- Metabolic, storage or infiltrative liver disorders.
- Unexplained persistent icterus or abnormal liver function tests.
- Suspected primary or secondary malignancy.

Serial biopsies are indicated for evaluation of therapeutic response in chronic liver diseases.

Contraindications include:

- Acute liver failure.
- Bleeding disorders.
- Tense ascites or peritonitis.
- Local infection, e.g. subphrenic abscess.
- Congestive hepatomegaly.
- Suspected vascular malformations* of liver
- Suspected hydatid disease*

(*absolute contraindications)

Pre-requisites: (a) informed consent, (b) coagulation profile*, (c) pre-procedure sedation and vagolytic agents, (d) pre-procedure ascetic tapping, if present, (d) blood grouping and cross-matching.

*Normal prothrombin time is an essential prerequisite for liver biopsy and all cases with abnormal PTT should receive three doses of IM Vitamin K (5 mg/dose) for normalization of coagulation profile with/without fresh frozen plasma just before biopsy.

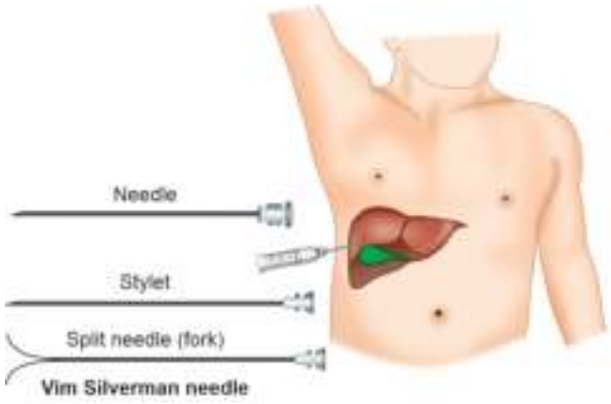

Fig. 32.23: **Liver biopsy.**

Pre-procedure vagolytic agent, e.g. IV atropine and sedation, e.g. phenobarbitone or chloral hydrate are indicated ~30 minutes before the procedure to reduce pain, anxiety and risk of vagal shock.

Instruments: Three types of needles are used for liver biopsy: (a) *tru-cut* needle, (b) *vim silverman* needle, and (c) *menghini's* aspiration needle. While Tru-cut needle is least traumatic and preferred choice, Vim Silverman needle is frequently used due to advantage of less failure rate and getting large liver tissue. Menghini's needle is rarely used in pediatric practice. Both needles are autoclavable or disposable. Liver biopsy needles can also be used for kidney and lung biopsy.

- **Tru cut needle** is a long, non-flexible metallic needle with two parts: (a) outer hollow needle with handle, and (b) inner solid needle with a gutter for biopsy tissue **(Fig. 32.23)**.
- **Vim Silverman needle** is a long, non-flexible metallic needle with three parts: (a) *cannula*, i.e. outer hollow needle, (b) *trochar*, i.e. inner solid needle, and (c) *bifid needle* for cutting the liver tissue **(Fig. 32.23)**.

Site: 9th–10th intercostal space in mid-axillary line after confirmation of liver dullness is preferred, though subcostal approach is used in select cases under ultrasonographic guidance.

Procedure: Important steps in liver biopsy by ***Vim-Silverman needle*** are as follows:

Restrain and position the patient in supine position on the edge of the bed with arms under head > clean the selected site with an antiseptic > drape the surrounding area > infiltrate 1–2% xylocaine for local anesthesia, > palpate the desired space > ask the patient to hold

the breath > insert the cannula with trochar for ~ 2 cm depth > remove the trochar, > insert the forked cutting needle through cannula for ~ 5 mm longer depth > rotate the bifid needle at 360° to cut the liver tissue > advance the cannula over needle > withdraw whole assembly > transfer the tissue between two blades of forked needle into preservative, e.g. formalin > seal the site with tincture benzoin.

Similar procedure is adopted by ***tru-cut needle*** except that - insert outer hollow needle with solid needle inside, till liver is penetrated > advance inner needle further into liver tissue for ~1 cm to collect the tissue sample in the gutter > advance outer needle to cover the gutter > withdraw whole assembly.

Failed liver biopsy indicates: (a) wrong technique, or (b) tough liver tissue, e.g. cirrhosis.

Complications include:

- Vagal shock during procedure,
- Local hematoma,
- Internal tissue injury or hemorrhage
- Infections, e.g. cholangitis/liver abscess and
- Precipitation of hepatic encephalopathy.

Post-procedure, the child should be observed for at least 24 hours for: (a) vital signs, (b) abdominal distension, (c) local hematoma formation, (d) signs of internal hemorrhage. A mild/anti-inflammatory agent may be given to reduce the pain and local inflammation.

Renal biopsy: Being an invasive procedure, renal biopsy is indicated only in selected cases with unexplained pathology, where precise diagnosis is essential for therapy/prognosis.

Indications include:

- Steroid-resistant nephrotic syndrome,
- Before starting calcineurin inhibitors therapy,
- Unexplained progressive/chronic renal failure,
- Unexplained/persistent hematuria or proteinuria,
- Suspected inherited/metabolic renal disease,
- Follow-up in chronic renal disease or renal transplant.

Contraindications include:

- Solitary functioning or ectopic kidney,
- Bleeding diathesis,
- Severe acute renal failure,
- Severe hypertension.

Procedure: A *tru-cut needle* or *Vim-Silverman needle with Franklin modification* is used for renal biopsy. Pre-procedure ultrasonographic localization of kidney (~2 cm below and medial to tip of 12th rib), is *must* before the procedure, as also the vagolytic/sedative medications. Important steps include:

Restrain and position the patient in prone position with head turned on one side and a rolled-up towel under abdomen > clean the USG marked site with an antiseptic > drape the surrounding area > local anesthesia with 1–2% xylocaine, > palpate the desired site > ask the patient to hold the breath > insert a 21 G long Needle (~8 cm) till kidney is pierced and needle moves with respiration (confirms the position) > mark the depth on needle and withdraw it > insert *tru-cut* or *Vim Silvermann needle* from the same track for similar depth > biopsy the tissue with procedure similar to that discussed for liver biopsy > withdraw whole assembly > transfer the collected tissue in proper preservatives* > seal the site with tincture benzoin.

*Obtained material should be sent for routine microscopic histology (in formalin), electron microscopy (in glutaraldehyde) and immunofluorescent studies (in saline).

Complications: Although transient microscopic hematuria for next 24–48 hours is inevitable after renal biopsy, other complications include:

- Persistent/gross hematuria
- Perirenal hematoma
- Renal or perinephric infection.

Complete bed rest and BP/output monitoring is essential for first 24 hours, to detect/treat complications.

Thoracocentesis is a common diagnostic/therapeutic procedure to obtain pleural fluid in effusions/empyema.

Indications: (a) diagnostic aspiration of fluid in suspected pleural effusion/empyema, (b) therapeutic drainage of large pleural collections, (c) rarely, to insert intra peural medications, e.g. antibiotics and steroids.

Site: Upper edge of lower rib in 7th or 8th intercostals space in posterior axillary line **(Fig. 32.24)**. Lower edge of the upper rib should be avoided to prevent injury to neighboring intercostal vessels.

Procedure: Restrain and position the child, preferably in sitting position > confirm the fluid level by ultrasonography *or* by percussion, > clean the selected site with an antiseptic > drape the surrounding area > infiltrate 1–2% xylocaine for local anesthesia, > palpate

Fig. 32.24: Thoracocentesis.

the desired space > ask the patient to hold the breath > insert a 16–18 gz. Needle attached to a syringe, perpendicular to the surface, till a *give-away* feel of entering pleural space > aspirate with gentle negative suction, > withdraw the needle and seal the site with tincture bezoin.

Note that:

- For therapeutic drainage of large effusions, a three-way stopcock must be fixed between the syringe and needle, to avoid repeated disengagement of syringe and risk of pneumothorax.
- Total aspirated volume in single sitting should not exceed > 5% of body weight.
- In cases of empyema, intercostal tube thoracotomy is necessary for continuous drainage of pus.

Complications include: (a) pneumothorax, (b) infection, and (c) traumatic puncture of liver/spleen or bleeding, and rarely, (d) sinus/fistula formation (in tubercular effusion).

Pericardiocentesis, i.e. drainage of pericardial fluid collections is a relatively risky procedure that should be performed under continuous monitoring of vital signs, ECG and pulse oximetry.

Indications: (a) *diagnosis* of the type of pericardial effusions, (b) *therapeutic* drainage of large effusions in cases with cardiac tamponade.

Site: Preferred site is just below and to the left of xiphoid process **(Fig. 32.25)**.

Procedure: Restrain and position the child in supine position> confirm the presence of pericardial fluid by ultrasonography > clean the selected site with an antiseptic > drape the surrounding area > infiltrate 1–2% xylocaine for local anesthesia, > ask the patient to hold the breath > insert a 16–18 gz. needle attached to a syringe at 45° to skin surface directed towards the left scapula > advance the needle till fluid is obtained or ECG changes appear (signs of contact with ventricular wall) > aspirate with gentle negative suction, > withdraw the needle and seal the site with tinc. bezoin.

Complications include: (a) arrhythmia, (b) traumatic hemopericardium, (c) myocardial injury. All patients should be kept under continuous supervision for 6–8 hours after the procedure.

Abdominocentesis is a common procedure to obtain ascitic fluid from peritoneal space.

Indications: (a) *diagnosis* of the type of ascites, (b) *therapeutic* drainage of large collections, leading to abdominal discomfort or respiratory embarrassment.

Site: Preferred site is the mid-way between umbilicus and anterior superior iliac spine on right side **(Fig. 32.26)**.

Procedure: Restrain and position the child, in supine position, > confirm the ascites by USG *or* by percussion, > clean the selected site with an antiseptic > drape the surrounding area > infiltrate 1–2% xylocaine for local anesthesia, > insert a 16–18 gz. Needle attached to a syringe, obliquely to prevent leakage of ascitic fluid, till fluid is obtained, > aspirate without suction, > withdraw the needle and seal the site with Tinc. bezoin.

Note that:

- For therapeutic drainage of large ascites, a three-way stopcock must be fixed between the syringe and needle to avoid repeated disengagement of syringe and risk of pneumoperitoneum.
- Total aspirated volume in one sitting should not exceed 5% of body weight.

Complications include: (a) trauma to deeper structures, e.g. intestines, (b) peritonitis.

Supra-pubic puncture is the safe and reliable method to obtain uncontaminated urine sample in infants.

Site: Midline, just above the pubic symphysis.

Procedure: Restrain and position the child in supine position, > confirm that the bladder is full by percussion

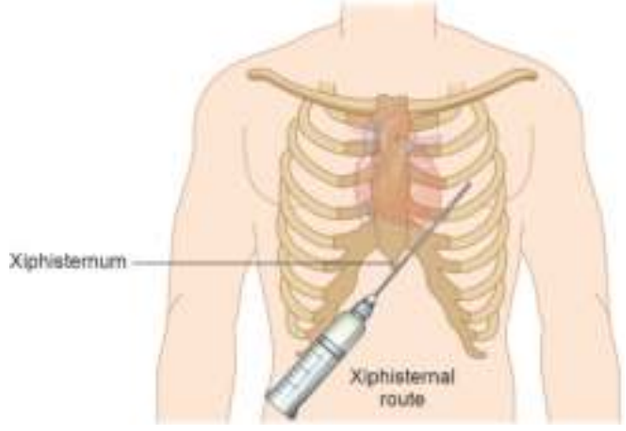

Fig. 32.25: **Pericardiocentesis.**

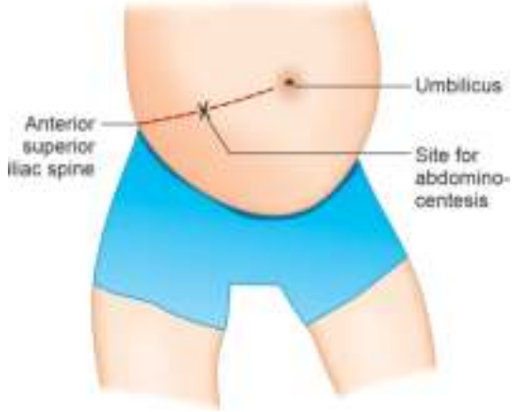

Fig. 32.26: **Abdominocentesis.**

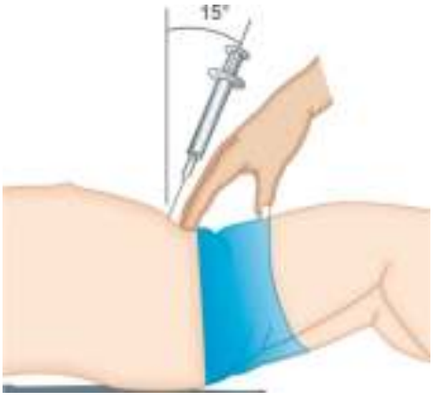

Fig. 32.27: **Suprapubic puncture.**

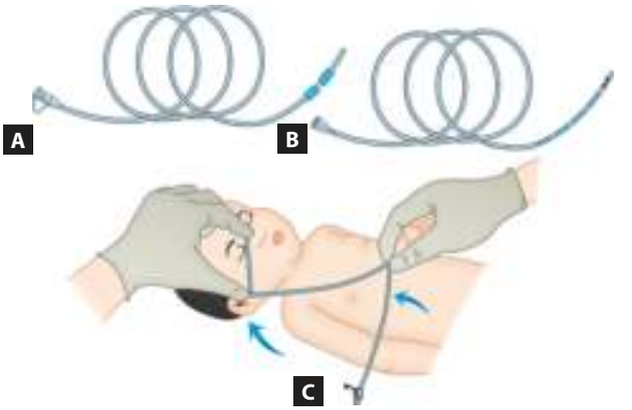

Fig. 32.28A to C: **(A) Ryles tube; (B) Infant feeding tube; (C) Method to determine desired length of nasogastric tube.**

> clean the selected site with antiseptic > drape the surrounding area > infiltrate 1–2% xylocaine for local anesthesia > insert a 21 gz needle/syringe, perpendicular to selected site for a depth of 2–3 cm, > aspirate the urine with gentle suction > withdraw the needle and seal the site with tincture benzoin **(Fig. 32.27)**.

32.7 FEEDING SUPPORT PROCEDURES AND DEVICES

This sub-chapter deals with some common feeding support devices in normal or sick children.

Nasogastric intubation is a common pediatric procedure for diagnostic as well as therapeutic purposes.

Indications: (a) *nasogastric feeding* or drug administration, (b) *gastric decompression*, e.g. in paralytic ileus, intestinal obstruction, GIT hemorrhage or peri-operative cases, (c) *gastric lavage* in poisonings, GIT hemorrhage, (d) *diagnostic gastric aspiration* in poisonings, hematemesis, AFB detection, and (e) for *diagnosis of esophageal anomalies*, e.g. esophageal atresia or strictures.

Contraindications: (a) corrosive acid/alkali poisoning, (b) deep necrotic esophageal ulcers.

Instruments: Two types of tubes are used for nasogastric intubation: (a) Ryle's tube or nasogastric tube in older children, and (b) infant feeding tubes for newborns, infants and younger children **(Fig. 32.28)**.

- **Nasogastric tube (Ryles tube)** is a long PVC tube of variable length and diameter (size 5–24 fG) with blind blunt tip on one end and stopper on other open end. The blind tip is filled with 2–3 lead shots and has 3–4 lateralized openings. Lead shots help in radiological localization of tube *in situ*, as well as facilitate tube insertion due to weight. Main body of the tube has three transverse markings, indicating the position of the tip of the tube in the gastrointestinal tract.
- **Infant feeding tube** is similar to Ryles tube with two differences: (a) thinner diameter (size 5–12 fG), and (b) absence of lead shots at the tip.

Sterilization: Both tubes are available as disposable presterilized units (gamma sterilization), in variable size, numbered according to their length and diameter.

Uses: While Ryle's tube is exclusively used for nasogastric intubation, infant feeding tube may also be used as: (a) umbilical cannula, (b) venesection cannula for CVP monitoring; (c) urinary catheter in infants, (d) nasal oxygen catheter, (e) suction catheter, or (f) tourniquet.

Procedure: Determine the proper length of tube, necessary to reach stomach* > lubricate the tip > inserted through nostril gradually, asking the patient to swallow it, till desired length is inserted > confirm it presence in stomach**.

**Desired length of the tube* that needs to be inserted, is determined by measuring the distance form tip of the nose to tragus and from tragus to xiphisternum.

***Intragastric position of tube* may be confirmed by: (a) aspiration of gastric contents, and (b) auscultation of bubbling sounds over stomach, when the air is pushed into the tube via a syringe.

Complications: (a) nasal trauma/hemorrhage, (b) esophageal ulceration, perforation or hemorrhage, (c) aspiration due to coiling of the tube in the pharynx.

32.8 URINARY CATHETERS AND DRAINAGE DEVICES

Catheters and procedures discussed in this section are usually used to collect diagnostic urine samples as well as to ensure adequate urinary drainage in sick children. Some catheters are also used for other purposes as well.

Simple rubber catheter is ~20–30 cm long rubber tube with a blunt tip and a slit-like opening (*eye*) just proximal and lateral to the tip **(Fig. 32.29)**.

Sterilization: Disposable catheters are preferred, though may be re-used after *boiling*.

Uses: Simple rubber catheter is a multi-purpose tube, used as:

Fig. 32.29: **Simple rubber catheter and flatus tube.**

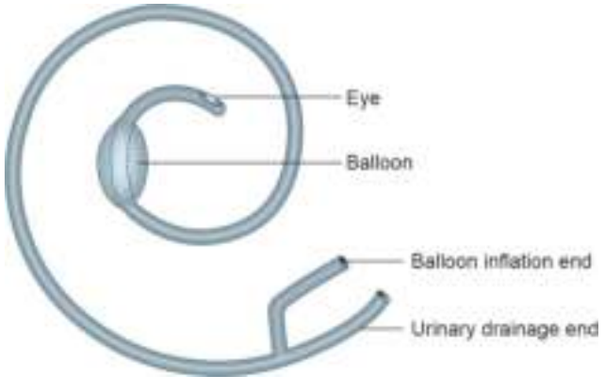

Fig. 32.30: **Foley's catheter.**

- *Non-retaining urinary catheter* to: (i) relieve acute urinary retention, (ii) differentiate between anuria and urinary retention, (iii) collection of urinary samples for cultures, and (iv) diagnose urethral strictures;
- *Flatus tube* to: (i) diagnose anal atresia (patency check) in newborns, (ii) relieve flatus, (iii) deliver bowel enema or bowel washes;
- *Limb tourniquet* for: (i) venipuncture (ii) minimize distal bleeding in emergency;
- *Nasal catheter* for: (i) nasal/oropharyngeal or endotracheal suction, (ii) nasal oxygen delivery, (iii) diagnosis of nasal atresia at birth (patency check).

Flatus tube is a simple rubber catheter with three differences: (a) longer length of ~50–70 cm, (b) thicker diameter of ~1 cm, and (c) bulbous tip with two side eyes to facilitate expulsion of gases **(Fig. 32.29)**. It may be re-used after cleaning with soap and water and sterilization by boiling.

Procedure: Flatus tube is inserted per rectally in left lateral position after proper lubrication for ~15–20 cm, while outer end is immersed under water to detect passage of gas bubbles.

Uses: Flatus tube is commonly used for: (a) gaseous deflation of bowels in paralytic ileus or toxic megacolon, (b) diagnosis of low bowel obstruction (absolute constipation), and (c) reduction of volvulus.

Foley's catheter is a self-retaining urinary catheter, available in *pre-sterilized* disposable pack with different sizes (No. 8–30), according to its diameter and length. It is a long latex rubber tube with following parts: (a) double-lumen body, (b) blind inner tip with side-slit (eye), (c) distensible balloon just proximal to the tip, and (d) outer end with two openings, one each for main catheter and balloon **(Fig. 32.30)**.

Procedure: The catheter with collapsed balloon is inserted via urethra after adequate lubrication, till free flow of urine begins. Subsequently, the balloon is distended with 30–40 ml of sterile water (and not the air that may introduce infection) to allow self-retention. While removing, balloon must be first deflated first to avoid urethral injury.

Uses: Foley's catheter is primarily used as *Self-retaining urinary catheter* in children with: (a) chronic bladder dysfunction or urinary retention, (b) urethral tear, to allow healing (conservative treatment with rail-road method), (c) post-genitourinary surgery for repeated bladder washes. Rarely, it is also be used for gastrojejunostomy feeding or as hemostatic temponade in emergency treatment of bleeding esophageal varices.

Complications of Foley's catheter include: (a) ascending urinary tract infection, (b) local urethral trauma during insertion or removal, leading to hematuria or late strictures, and (c) impacted balloon.

Malecot's catheter is a self-retaining catheter, available in different sizes (No. 8–44), according to its diameter. It is a long *India-rubber* tube with three main parts: (a) blind tip with slit-opening on the side, i.e. *eye*, (b) a flower-like structure just proximal to the tip that allows self-retention, and (c) tubular single-lumen body **(Fig. 32.31)**. Before insertion, the flower has to be collapsed by stretching the catheter over an *introducer*. It may be re-used after sterilization by autoclaving.

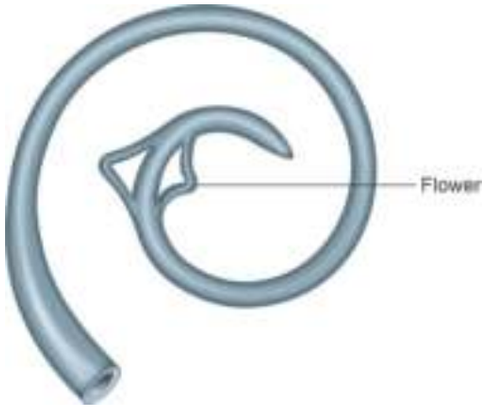

Fig. 32.31: **Malecot's catheter.**

Fig. 32.32: **Condom catheter.**

Uses: Malecot's catheter is mainly used as self-retaining catheter for:

- Intercostal chest drainage in empyema/pneumothroax,
- Suprapubic cystostomy for urinary retention when urethral catheterization is not possible,
- Post-operative drainage of deep-seated abscesses, e.g. perinephric abscess/hematoma,
- For condom catheterization (*see* below).

Malecot's catheter is *no longer used as self-retaining urinary catheter*.

Condom catheter comes in a disposable readymade pack or may be prepared by making a small nick at the tip of a condom and inserting a Malecot's catheter through this nick in such a way that the catheter flower rests on this nick **(Fig. 32.32)**. The other end of catheter is connected with a urine collection bag via PVC tubing.

Uses: Condom catheter is used as a non-invasive urine collecting device in: (a) cases with urinary incontinence to prevent soiling, (b) young infants or unconscious children to monitor urinary output. Being non-invasive, the risk of urinary tract infection is minimal with condom catheterization.

32.9 GENERAL MONITORING EQUIPMENT

Pediatric weighing scales: Precise weight record is an essential component of pediatric care for: (a) growth monitoring, and (b) calculation of drug dosages.

Commonly used Weighing scales, in order of preference may be broadly divided into: (a) electronic scales, (b) beam-balances, and (c) spring balances **(Fig. 32.33)**. Spring balances, though convenient to use in field-work, should not be used in routine practice due to frequently faulty readings after overuse of springs. Different types of beam/electronic weighing balances are available for infants (Maximum capacity 8–20 kg) and older children, with minor manufacturer's variations. A beam-type infant weighing scale usually has a least value of 20 gm, while those for older children record minimum weight difference of 100 gm. Before weighing, the zero error should also be checked and corrected if necessary, with the use of adjusting screw, provided in all balances.

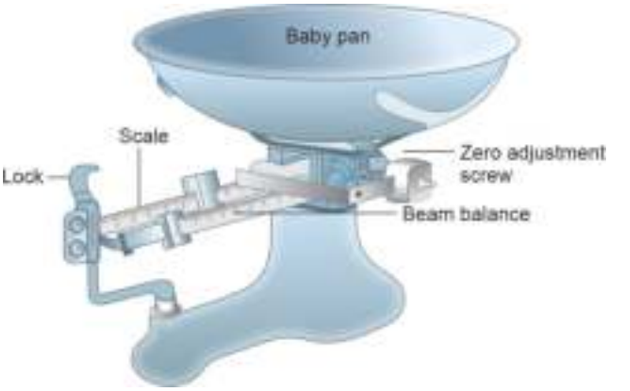

Fig. 32.33: **Weighing balance.**

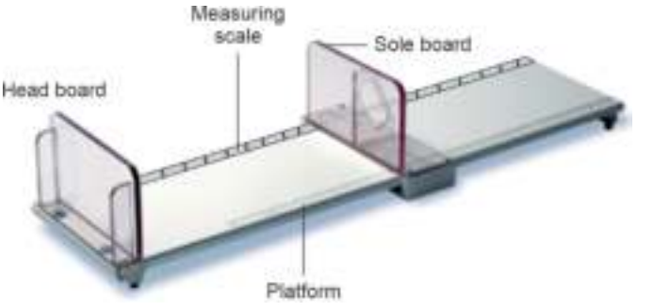

Fig. 32.34: **Infantometer.**

Infantometer is a wooden device to measure the length of children <2 years; with three parts: (a) graduated wooden platform to place the infant in supine position, (b) fixed sole board and (c) sliding head board to adjust according to the child/s length **(Fig. 32.34)**. Baby should be placed over infantometer platform in a correct position-straight head, fully extended legs and feet at right angles to legs, before adjusting the headboard to record the length on graduated scale.

Thermometers: Two types of thermometers are commonly used to record body temperature: (a) mercury-based, and (b) digital thermometers. Mercury-based thermometers are being gradually phased out due to environmental concerns of mercury leak.

- *Mercury-based thermometers* have two parts: (i) metallic bulb filled with mercury, and (ii) long graduated glass tube. On contact with body, mercury in the bulb expands and rises into glass tube. Extent of rise on graduated scale denotes body temperature. This expanded mercury column must be jerked back into the bulb (at least 2° below normal) before re-use.

  Mercury based thermometers include: (a) standard *clinical thermometers*, and (b) low-reading *Rectal thermometers*. Rectal thermometers are shorter tubes with round or pear-shaped bulb without constriction at the neck, which can detect hypothermia < 35°C, specially in newborns. However, rectal thermometers

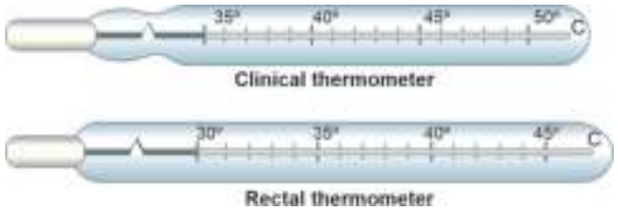

Fig. 32.35: **Clinical and rectal thermometer.**

Fig. 32.36: **Finger pulse oximeter.**

are rarely used at present due to risk of trauma and infection **(Fig. 32.35)**.

- *Digital thermometers* are mercury-free and use many types of sensors, e.g. resistance temperature detectors, thermocouple and thermistor, to provide direct digital display of the temperature after pre-determined time.

In children, temperature may be recorded at various sites, preferably using a digital thermometer, e.g. axilla, groin, oral cavity and rectum. Rectal temperature is 1°F higher than oral temperature, which in turn is 1°F higher than surface (axillary/groin) temperature. Thermometer should be kept *in situ* for 3–5 minutes for surface temperature and 1–2 minutes for core (rectal/oral) temperature.

After use, thermometers should be washed, wiped and stored in a glass jar partly filled with a disinfectant like 70% isopropyl alcohol with 1% iodine. The jar should have a piece of cotton wool at the bottom to prevent breakage. Individual patient-specific thermometers are preferred at present to avoid cross infections.

BP instrument and cuffs are available in different sizes ranging from 3.5 cm and 4.5 cm (for preterms and term newborns, respectively) to maximum size of 17.5 cm for use in adolescents. Correct cuff size is important to measure the BP as smaller cuff tends give higher readings and vice versa. An ideal cuff size should cover ~2/3rd of arm length (Ch 17.12).

Two types of portable BP instruments are in use at present: (a) conventional mercury-based sphygmomanometers, and (b) digital BP monitors. However, mercury-based thermometers are being gradually phased out due to environmental concerns of mercury leak.

Digital BP monitors work on oscillometric method of BP measurement and correct BP measurement practices should be followed for their use (Ch 17.12).

Finger pulse oximeter is a simple non-invasive method to monitor percentage of hemoglobin saturated with oxygen (SaO_2).

It consists of a patient's probe attached to finger or earlobe and a central data processing unit with SaO_2 display. The clip-like probe has a light source on one lip and a photosensor on other lip, to monitor the intensity of light traversed through pulsating capillary bed **(Fig. 32.36)**.

Accuracy of pulse oximeter is high (+ 2%) till SaO_2 is >70% but tends to be unreliable below these values. False values may also be obtained due to: (a) low capillary perfusion, e.g. shock, (b) presence of abnormal hemoglobin, e.g. methemoglobin or carboxyhemoglobin, (c) optic interference with external light source, e.g. phototherapy or warmers.

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CHAPTER

33

Drugs and Medications

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Drug prescription in pediatrics is a complex issue, considering major differences in *pharmacokinetics* and *pharmacodynamics* of various drugs and formulations between adults and children. This chapter provides some essential information on pediatric pharmacology.

Drug dosage in children is generally calculated according to body weight or body surface area. Surface area may be calculated by *Mosteller's formula* or more reliably, with the help of a nomogram **(Fig. 33.1)**.

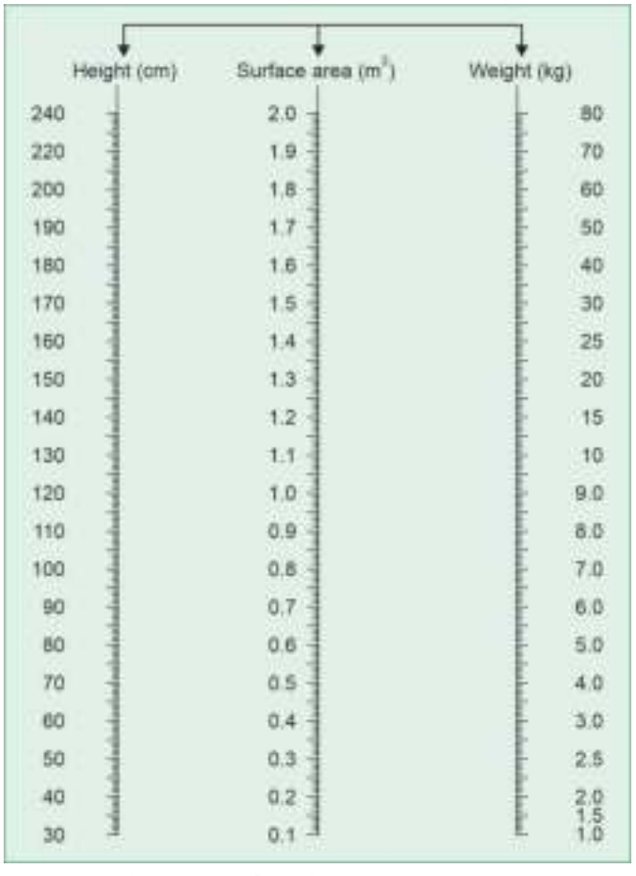

Fig. 33.1: Body surface area nomogram.
Join the values on scales representing child's height (Left) and weight (Right) with a ruler. The point of crossing the middle scale by this ruler represents body surface area in m^2.

Mosteller's formula =

$$\text{Surface area } (m^2) = \sqrt{Height\ (cm) \times Weight\ (kg) / 3600}$$

General dosage guidelines, mechanism of action, common side effects and essential precautions related to common drugs used in pediatric practice are presented in following sections. Note that…

- This is not an exhaustive list and only commonly used drugs in children have been included.
- Dosages listed here are for general pediatric population and not for specific subsets, e.g. preterms and newborns, unless specifically indicated.
- All doses are approximate, based on general recommendations in standard textbooks, which may vary from source to source. For detailed information, refer to manufacturer's brochure.
- Dosages are generally expressed according to body weight/day (xxx/kg/d), followed by frequency of doses in hours, e.g. q6/8/12/24hr. (If a dose in mentioned as daily dose, it needed to be divided as per frequency to calculate each dose).
- Only important adverse events have been listed. For details, refer to manufacturer's brochure.
- Following abbreviations have been used:
  AE: Adverse events, **d:** day, **kg:** kilogram body weight, **hr:** hour, **IM:** Intramuscular, **IV:** Intravenous, **mg:** milligram, **µg:** microgram, **m^2:** per square meter body surface area, **MoA:** Mechanism of action, **PO:** Per oral, **PR:** Per-rectal, **Q4/6/8/12/24 hr:** Frequency of divided doses, **SC:** subcutaneous, **SL:** Sublingual, **U/IU:** Units/International units, **Wk:** weeks

33.1 ANTI-BACTERIAL THERAPY

Choice of the antibiotics in bacterial infections depends on causative organism, site and severity of infection, *in vitro* sensitivity results and patient's characteristics, e.g. age, hepatorenal status, etc.

β-lactam antibiotics are those antibiotics which exert antibacterial activity via a β-lactam ring in their structure, e.g. penicillins, cephalosporin, monobactum and carbapenems. These antibiotics are rapidly inactivated by β-lactamase enzymes, e.g. *Penicillinase*, *cephalosporinase*, etc. produced by some pathogens.

Majority of gram-negative bacteria, staphylococci, anaerobes and even mycobacteria produce these enzymes. Consequently, β-lactam antibiotics are ineffective against these pathogens, unless combined with a β-*lactamase inhibitor*, e.g. clavulinic acid, sulbactum or Tazobactum. Streptococci, pneumococci and most enterococci do not produce β-lactamase enzymes.

Penicillin group of antibiotics contain a common nucleus (6-aminopenicillanic acid) and include Natural penicillins as well as Semi-synthetic penicillins. Benzyl penicillin was the earliest discovered antibiotic extracted from a natural fungal source by Sir Alexander Fleming in 1924.

Mechanism of Action (MoA): All Penicillins are *bactericidal*, inhibiting cell wall synthesis or activating the enzymes that destroy bacterial cell walls. All of them are β-*lactam* antibiotics (penicillinase-sensitive), *except* methicillin and its derivatives, e.g. cloxacillin and ticarcillin.

Antimicrobial spectrum:

- *Natural penicillin* and its repository preparations have narrow spectrum of activity against gram-positive cocci and bacilli,gram-negative cocci, anerobes and spirochetes. These drugs are ineffective against gram negative bacilli and penicillinase-producing pathogens.
- *Broad-spectrum penicillins* also cover gram-negative bacilli but not the penicillinase-producing organisms, unless combined with a β-lactamase inhibitor. Ampicillin is the drug of choice for Listeriosis.
- *Penicillinase-resistant penicillins*, e.g. cloxacillin are mainly used against coagulase-positive staphylococci. However, these agents are ineffective against Coagulase-negative staphylococci (CONS) and enterococci.
- *Extended-spectrum penicillins* are highly effective against pseudomonas and anerobic infections but less effective against gram-positive infections, specially staphylococci.

Doses: *See* Table 33.1.

Adverse-effects (AE): *Anaphylaxis* is the most serious adverse event of parenteral natural penicillins (~ 1%) and an intradermal sensitivity test is advised before these injections.

Minor hypersensitivity reactions, e.g. urticaria or rash, are common with other penicillins as well but anaphylaxis is rare and sensitivity test is not indicated. However, these drugs should be avoided in cases with history of penicillin allergy. A generalized maculopapular rash is common with ampicillin, specially when used in cases of Infectious mononucleosis or other viral infections.

Drug-induced diarrhea due to altered colonic flora is common, specially with ampicillin, which may be minimized by simultaneous probiotic therapy. *Pseudomembranous colitis* is a rare complication of ampicillin therapy.

TABLE 33.1: Penicillins

Drug	*Dose/day*
a. Natural Penicillins	
Benzyl Penicillin G	IV 1,00,000–4,00,000 U/kg/d q6hr
Procaine penicillin G	IM 50,000–1,00,000 U/kg/d q12hr
Benzathane penicillin G	IM 6,00,000–12,00,000 U q3wks
Phenoxymethyl Penicillin V	PO 10–15 mg/kg/d q6hr
Broad Spectrum Aminopenicillins	
Ampicillin ± Sulbactum	IV/PO 100–200 mg/kg/d q6-8hr
Amoxicillin ± Clavulanate	IV/PO 25-50 mg/kg/d q8hr
Penicillinase-resistant (Antistaphylococcal) penicillins	
Methicillin	IV 150-200 mg/kg/d q6hr
Cloxacillin	IV/PO 50-100 mg/kg/d q6hr
Nafcillin	IV100-200 mg/kg/d q6-8hr
Oxacillin	PO 50-100 mg/kg/d q6hr
Extended-spectrum (Antipseudomonas) Penicillins	
Ticarcillin ± Clavulanate	IV 200-400 mg/kg/d q6hr
Carbenicillin	IV 400-600 mg/kg/d q6hr
Piperacillin ± Tazobactum	IV 200-300 mg/kg/d q6hr

Note: All IV drugs may also be given IM.

Cephalosporins include antibiotics with a common nucleus (7-Aminocephalosporanic acid). Although penicillinase-resistant, these antibiotics are inactivated by other β-lactamase enzymes, e.g. cephalosporinase.

MOA: All cephalosporins are bactericidal, inhibiting cell wall synthesis.

Antimicrobial spectrum:

- *First-generation cephalosporins* have a microbial spectrum similar to penicillins, while *second-generation cephalosporins* have greater activity against gram-negative bacilli. Both first and second generation cephalosporins (*except cefuroxime*) do not cross blood-brain barrier and hence, ineffective in CNS infections.
- *Third-generation cephalosporins* have broader spectrum, but with limited activity against staphylococci. These agents cross blood-brain barrier and commonly used for CNS infections.
- *Fourth-generation cephalosporins* have enhanced activity against pseudomonas and staphylococci but do not cover anerobes.
- *Fifth-generation cephalosporins* are broad-spectrum, but predominantly used for methicillin-resistant *Staph.*

aureus (MRSA) in cases with renal dysfunction, when vancomycin/Teicoplanin cannot be used.

Doses: *See* **Table 33.2**.

AE: About 10% of penicillin-allergic patients show cross-sensitivity to cephalosporins, which should be avoided in these cases.

Other important adverse effects include—(a) diarrhea, (b) drug fever and (c) nephrotoxicity with some parenteral cephalosporins. These agents should be used with caution in cases with renal damage or co-aminoglycoside therapy.

Glycopeptide antibiotics (Vancomycin and Teicoplanin) are commonly used anti-staphyloocccal agents, specially in cases allergic to penicillins/cephalosporins. Teicoplanin is longer-acting and less nephrotoxic than vancomycin.

MoA: These antibiotics are bactericidal by inhibiting cell wall synthesis like penicillins/cephalosporins, but do not contain β-lactam ring.

Spectrum: Apart from excellent activity against *staphylococcal infections* including MRSA, these antibiotics also covers gram-positive cocci and bacteria, gram-negative cocci and gram-positive anerobes. Gram-negative bacilli and anerobes are usually resistant to them. These antibiotics are also preferred for: (a) CSF shunt infections (due to *Staph. epidermidis*), (b) pseudomembranous colitis (due to *C. difficile*), and (c) infections in neutropenic hosts

Doses:

- *Vancomycin* IV 40–60 mg/kg/d q6–8 hr
- *Teicoplanin* IV 10 mg/kg/dose 12-hrly × 3 doses, followed by 6–10 mg/kg/d q24hr

AE: Nephrotoxicity, Red-man syndrome (Generalized flushing and erythema), Hypersensitivity reactions, Thrombophlebitis.

Aminoglycosides are natural (Gentamicin) or semi-synthetic (amikacin) drugs, which are not absorbed orally and hence, given parenterally. Some aminoglycosides, e.g. Neomycin, are used only topically or given orally for bowel sterilization.

MoA: Aminoglycosides are *bactericidal*, which inhibit *or* alter bacterial protein synthesis. Natural resistance to these antibiotics is common due to mutations in the organisms.

Spectrum: Aminoglycosides are highly effective against *gram-negative bacilli and mycobacteria*, but with poor coverage against other aerobes/anerobes. Hence, these agents are often used in combination with penicillins or cephalosporins. Some aminoglycosides are also effective against penicillinase-producing staphylococci.

Doses: *See* **Table 33.3.** However, these aminoglycoside doses needs modification according to serum creatinine levels in cases with renal damage.

AE: *Vestibule-cochlear damage* and *Nephrotoxicity* are most serious adverse events with aminoglycoside therapy. Vestibular toxicity (vertigo) is predominant with streptomycin, while other aminoglycosides predominantly cause cochlear damage on prolonged use (deafness).

Other important adverse events include rashes, drug fever (5%) and rarely, skeletal muscle weakness.

TABLE 33.2: Cephalosporins

Drug	*Dose/day*
First-Generation	
Cephalaxin	PO 25–100 mg/kg/d q6hr
Cefadroxil	PO 30–50 mg/kg/d q12hr
Cefazolin	IV 50–100 mg/kg/d q8hr
Second-generation	
Cefaclor	PO 20–40 mg/kg/d q8hr
Cefuroxime	IV 50–100 mg/kg/d q8h PO 20–30 mg/kg/d q8hr
Cefamandole	IV 50–150 mg/kg/d q8hr
Third-eneration	
Cefotaxime	IV 100–200 mg/kg/d q8-12hr
Cefoperazone ± Sulbactum	IV 100–150 mg/kg/d q8-12hr
Ceftriaxone	IV 50–100 mg/kg/d q12hr
Ceftazidime	IV 50–150 mg/kg/d q8-12hr
Cefixime	PO 8–10 mg/kg/d q12hr*
Cefpodoxime	PO 10 mg/kg/d q12hr
Cefdinir	PO 14 mg/kg/d q12hr
Cefprozil	PO 15–30 mg/kg/d q 8–12hr
Fourth-generation	
Cefepime	IV 100–150 mg/kg/d q8–12hr
Cefpodoxime	PO 8–10 mg/kg/dq12hr
Fifth-generation	
Ceftolozone ±Tazobactum	IV 90 mg/kg/d q8hr (slowly)
Ceftaroline	IV 24–36 mg/kg/d q8hr (slowly)

Note: All IV drugs may be given IM.* 20 mg/kg in enteric fever

TABLE 33.3: Aminoglycosides

Drugs	*Dose/day*
Streptomycin	IM 20–40 mg/kg/d q24hr*
Amikacin	IV 15–20 mg/kg/d q8–12hr
Gentamycin	IV 5–7.5 mg/kg/d q8–12hr
Kanamycin	IV 15–20 mg/kg/d q8–12hr
Tobramycin	IV 5–7.5 mg/kg/dd q8–12hr
Netilmycin	IV 5–7.5 mg/kg/d q12hr

Note: All IV drugs may be given IM

TABLE 33.4: Macrolides

Drugs	*Dose/day*
Erythromycin	PO 30–50 mg/kg/d q6–8hr (Rarely IV 5mg/kg TDS over 20-30 min)
Azithromycin**	PO 10 mg/kg/d q24hr*
Roxithromycin	PO 5 mg/kg/d q12hr
Clarithromycin**	PO 15 mg/kg/d q12hr

*PO/IV 20 mg/kg/d q12-24hr in enteric fever
**Also used for MAC prophylaxis (PO 15-20 mg/kg/week).

Macrolides antibiotics are almost always used orally and include *short-acting* Erythromycin or *longer-acting* Roxythromycin or Azithromycin, etc.

MoA: All Macrolides are *bacteriostatic*, which act by inhibiting protein synthesis.

Spectrum: These agents are specially active against *gram-positive cocci, mycoplasma, chlamydial and treponemal infections*. Generally used as oral alternatives to penicillins. Azithromycin is also effective against some gram-negative organisms, including enteric fever. Spiramycin is a weak macrolide, used mainly for toxoplasmosis. Clarithromycin is also used for prophylaxis against Mycobacterium avium complex (MAC) in immunocompromized children.

Doses: *See* **Table 33.4**

AE: *Gastrointestinal upset,* e.g. gastritis/vomiting, and *Hepatotoxicity* (intrahepatic cholestasis) are predominant adverse events of macrolides,These agents slow-down aminophylline metabolism and should be used with caution in cases on amiophylline.

Quinolones and fluoroquinolones include four different generations of antibiotics, of which only first two are generally used in children, specially for enteric fever, urinary tract infections, bacterial diarrhea. Newer generation Levofloxacin and Moxifloxacin are cornersone of treatment for MDR-TB, though resistance to them is also emerging.

MoA: Quinolones are *bactericidal*, preventing nucleic acid synthesis by inhibiting some enzymes required for maintenance of microbial DNA structure.

Spectrum: These agents are *broad-spectrum*, effective against both gram-negative and gram-positive pathogens, including those resistant to penicillins, cephalosporins and aminoglycosides. Quinolones are also effective against mycobacteria but with poor activity against anerobes and MRSA infections.

Doses: *See* **Table 33.5.**

AE: GITupset, Arthropathy. Potential *risk of damage to growing articular cartilage* is the major concern for wider use of quinolones, which should be avoided in younger children except as second-line drugs.

TABLE 33.5: Quinolones and fluoroquiolones

Drug	*Dose/day*
Quinolones	
Nalidixic acid	PO 50–60 mg/kg/d q8hr
Second generation Fluoroquinolones	
Ciprofloxacin	PO 20–40 mg/kg/d q12hr IV 10–20 mg/kg/d q12hr (max 800 mg/d)
Ofloxacin	PO 15 mg/kg/d q12hr IV 5–10 mg/kg/d q12hr
Norfloxacin	PO 10–15 mg/kg/d q12hr
Pefloxacin	PO 12 mg/kg/d q12hr
Third Generation Fluoroquinolones	
Levofloxacin	PO/IV 10 mg/kg/d q24hr (20 mg/kg < 5 yr)
Sparfloxacin	PO 4 mg/kg/d q24hr
Fourth generation Fluoroquinolones	
Moxifloxacin	PO 7.5–10 mg/kg OD
Gatifloxacin	PO 10 mg/kg/d q24hr

Tetracyclines are used sparingly in children due to potential risk of drug deposition in teeth and bones, leading to dental staining, enamel hypoplasia and stunting.

MoA: Tetracyclines are *bactericidal* drug, inhibiting bacterial protein synthesis.

Spectrum: Although *broad-spectrum*, tetracyclines are used for limited indications in children, e.g. cholera, plague, Leptospirosis and Rickettsial fevers (drug of choice). Tigecycline is a newer tetracycline, also effective against MRSA and resistant nosocomial infections with E.coli and Klebsiella.

Doses:

- *Tetracycline:* PO 25–50 mg/kg/d q6hr, or IV 15–25 mg/kg/d q8–12hr.
- *Doxycycline:* PO 2–5 mg/kg/d q12–24hr
- *Tigecycline* IV 2.4 mg/kg/d q12hr (max 50 mg/d)

AE: Dental (enamel) staining, impaired bone growth.

Carbapenems are β-lactam antibiotics but are relatively resistant to β-lactamase.

MoA: Carbapenem are potent *bactericidal* agents, inhibiting cell wall synthesis

Spectrum: Carbapenems are *broad-spectrum*, mainly effective against *Gram-negative* aerobes, including pseudomonas, gram positive aerobes and most anerobes. However, these drugs are not effective against mycoplasma and chlamydia organisms. Imipenem + Cilastatin is the drug of choice for ESBL organisms.

Doses:

- *Imipenem + Cilastatin:* IV 60–100 mg/kg/d q6–12hr
- *Meropenem:* IV 60–120 mg/kg/d q8hr.

- *Ertapenem:* IV 15–30 mg/kg/dq12hr (not < 3 mo)
- *Faropenem*: PO 30 mg/kg/d q8–12hr

AE: Hypersensitivity reactions, GIT disturbances including pseudomembranous colitis, rarely seizures.

Monobactums, e.g. Aztreonam, are also β-lactam antibiotics, usually used to serious *gram-negative* infections, e.g. pseudomonas and enterobacteria, commonly of nosocomial origin.

MoA: Aztreonam is a potent *bactericidal* agent, which inhibit cell wall synthesis.

Spectrum: Aztreonam is selectively active against *Gram-negative* aerobic bacteria and inactive against Gram-positive bacteria.

Dose: IV Aztreonam 90–120 mg/kg/d q6–8hr.

AE: Hypersensitivity reactions, e.g. rash, thrombophlebitis.

Lincosamide group include two commonly used antibiotics - Lincomycin and clindamycin, later being more effective and preferred.

MoA: Both drugs are *bacteriostatic* but can be bactericidal in higher doses by inhibiting bacterial protecin synthesis.

Spectrum: Lincosamides are mainly effective against *gram-positive cocci* (including penicillinase producers), commonly used as second-line drug for resistant infections due to these pathogens or in penicillin allergy. Two important indications include orthopedic infections due to better bone penetration and fecal-contaminated peritonitis.

Doses:

- Lincomycin: PO 30 mg/kg/d q6hr, *or*
  IV 20 mg/kg/d q12hr
- Clindamycin: IV/PO 20–40 mg/kg/d q6–8hr

AE: GIT upset, rarely pseudomembranous colitis, Thrombocytopenia, Hypersensitivity reactions, e.g. Steven Johnson syndrome or *Drug-induced Eosionphilia with systemic symptoms* (DRESS), etc.

Linezolid is an oxazolidinone antibiotics (others include Tedizolid), which blocks the bacterial protein synthesis. It is mainly effective against MRSA, (which are also resistant to vancomycin) and penicillin-resistant pneumococci. It is not effective against gram-negative pathogens. Further, there is no cross-resistance to other antibiotics.

Dose: PO/IV 10 mg/kg/dose q12hr.

AE: GIT disturbances, Thrombocytopenia.

Colistin is a *bactericidal* antibiotic, which penetrates into and disrupts the bacterial cell membrane. It is mainly active against gram-negative infections, with no effect of Gram-positive and anerobic infections. Colistin is sparing used in highly resistant nosocomial infections in intensive care units.

Dose: PO 2.5–5 mg/kg/d q6–12hr (max 5 mg/kg/d)

AE: Nephrotoxicity, parasthesia, Neurotoxicity

Polymyxin acts on bacterial cell wall and is sparingly used in intensive care units with highly resistant nosocomial gram negative infections, specially due to Pseudomonas auroginosa.

Dose: IV 15,000- 25,000 U/kg/d q12hr
(Often used with intrathecal 50000 IU alternate day in meningitis)

AE: Nephrotoxic, Dizziness.

Chloramphenicol is a broad-spectrum *bacteriostatic* agent, predominantly effective against gram-negative pathogens. However, drug-resistance is common. Considering potential risk of bone marrow toxicity, it is now used only for selected indications (in young children, when tetracycline is contraindicated).

Dose: IV/PO 50–100 mg/kg/d q6–8hr.

AE: *Bone marrow depression* is the potentially fatal risk, which may be dose-related or idiosyncratic (1:10,000–50,000). Other complications include – *Drug fever, Drug rash* and *Gray-baby syndrome* in newborns.

Sulfonamides are predominantly *bacteriostatic* antimicrobials, inhibiting Nucleic acid synthesis (Anti-folate agents). These drugs are classified according to duration of action as: (a) *short acting,* e.g. sulfadiazine, sulfadimidine, sulfamethazole, (b) *intermediate acting*, e.g. sulfamethoxazole, and (c) *long-acting,* e.g. sulfadimethoxine.

Sulfonamides are rarely used at present due to widespread resistance and high risk of allergic skin reactions, e.g. Steven-Johnson syndrome, except in selected indications, e.g. (a) ulcerative colitis (sulfasalazine), and (b) some protozoal infections, e.g. Toxoplasmosis and malaria (along with pyrimethamine).

Doses: see specific chapters.

AE: Allergic reactions ranging from mild urticaria or fixed drug eruptions to severe Steven-Johnson syndrome, Sulfa drugs also displaces bilirubin from binding sites and should not be used in newborns.

Cotrimoxazole, is a combination of sulfamethoxazole with trimethoprim (5:1).

MoA: The combination acts synergistically to block endogenous synthesis of folic acid from paraaminobenzoic acid (PABA), necessary for bacterial growth (DHFR inhibitor).

Uses: It is a broad-spectrum, low-cost antibacterial, mainly used in prevention and treatment of urinary tract infections, respiratory tract infections, enteric fever, bacillary dysentery and Pneumocystis carinii pneumonia (also for prophylaxis).

Dose: Generally, PO 5–8 mg/kg of Trimethoprim q12hr or according to indications, as follows:

- PCP treatment: 15–20 mg/kg/d of TMP q6–8hr
- PCP prophylaxis: 5 mg/kg of TMP on alternate day
- UTI prophylaxis 1–2 mg/kg/day

AE: Skin-allergic reactions ranging from mild urticaria or fixed drug eruptions to severe Steven-Johnson syndrome, Folic acid deficiency, Pancytopenia. Sulfamethoxazole displaces bilirubin from binding sites and should not be used in newborns.

Nitrofurans are broad-spectrum antimicrobials, rarely used at present due to common resistance, adverse effects and availability of better options.

Uses: Two common uses include: (a) *Nitrofurantoin* as urinary antiseptic in chronic UTI, and (b) *Furazolidone* in bacterial diarrhea/dysentery and giardiasis.

Dose:

- *Nitrofurantoin:* PO 5–7 mg/kg/d q8hr (UTI Treatment). PO 1–2 mg/kg/d q24hr HS (UTI prophylaxis).
- *Furazolidone:* PO 6 mg/kg/d q8hr.

AE: Gastrointestinal upset, Hemolysis in G6PD deficiency, Immunological reactions, e.g. pulmonary fibrosis, chronic active hepatitis and SLE-like reaction.

33.2 ANTI-TUBERCULAR AGENTS

Antitubercular drugs may be classified according to: (a) *Mechanism of action*, e.g. bactericidal or bacteriostatic, (b) *Site of action*, i.e. extracellular or intracellular and (c) *Predominantly targeted bacilli*, i.e. Rapid-multipliers, Slow-multipliers or Dormant. While treatment of drug-sensitive tuberculosis at present involves use of only four drugs (HRZE),many other drugs are used for treatment of drug resistant tuberculosis (DRTB or MDR TB).

Amikacin

Uses: MDR Tuberculosis, General antibiotic (Ch 33.1)

MoA: Aminoglycoside antibiotic, Bactericidal

Dose: IM 15–20 mg/kg q24hr (max 1000 mg)

AE: Nephrotoxicity

Bedaquiline

Uses: MDR Tuberculosis (>12 years of age*)

MoA: inactivates ATP-synthatase enzyme of mycobacteria

Dose: PO 200 mg/dose q24hr × 2 wks, then -
100 mg/dose thrice a week × 22 wks
(Double these doses in children >30 kg)

AE: Prolong QTc interval, Chest pain, Hemoptysis

**Approved for children >12 yrs only but may be used in those >15 kg body weight.*

Avoid milk or large fatty meals with drug.

Capreomycin

Uses: MDR Tuberculosis

MoA: Aminoglycoside antibiotic, Bactericidal

Dose: IM 15 mg/kg/d q24hr

AE: Vestibular toxicity, Deafness, Nephrotoxicity.

Clofazamine

Uses: MDR-TB, Leprosy

MoA: Bactericidal, binds to mycobacterial DNA

Dose: As per indications:

- *TB:* PO 2–5 mg/kg Alt day ((Thrice a week < 5 kg)
- *Leprosy:* 6 mg/kg/month + 1 mg/kg Alternate day

AE: Reddish-dark pigmentation of skin and secretions

Cycloserine

Uses: MDR Tuberculosis

MoA: Bacteriostatic

Dose: PO15–20 mg/kg q24hr

AE: Psychosis, Photosensitive rash, Megaloblastic anemia.

Delamanid

Uses: MDR Tuberculosis (> 5 years of age*)

MoA: Blocks formation of mycolic acid, essential for MTB survival

Dose: PO 50 mg/dose q12hr × 24 wks (100 mg/dose q12hr >12 yrs)

AE: Headache, Parasthesia, Tremors, Psychiatric problems

**Approved by WHO for age 3–5 yrs, but not in India*

Avoid milk or large fatty meals with drug.

Ethambutol (ETB)

Uses: Tuberculosis treatment (First-line and MDR)

MoA: Bacteriostatic

Dose: PO 20 (15–25) mg/kg q24hr

AE: Optic neuritis*, Peripheral neuritis, Dizziness.

**Periodic fundus exam is required.*

Ethionamide/Proethionamide

Uses: MDR Tuberculosis

MoA: Bacteriostatic.

Dose: PO 15–20 mg/kg/d q8–12hr

AE: Hepatotoxicity, Optic neuritis, Pyridoxine deficiency.

Isoniazide (INH)

Uses: Tuberculosis - Treatment and Prevention

MoA: Bactericidal

Dose: As per indications:
- General: PO 10 (7–15) mg/kg/d q24hr (max 300 mg/d)
- High-dose: PO 15–20 mg/kg/d q24hr in MDR-TB
- Prevention: PO 10 mg/kg/d q24hr (5 mg/kg >10 yr)

AE: Peripheral neuritis, Hepatitis, Psychosis.

Kanamycin

Uses: MDR Tuberculosis, General antibiotic (Ch 33.1)

MoA: Aminoglycoside antibiotic, Bactericidal

Dose: IM 15–20 mg/kg/d q24hr (max 1000 mg)

AE: Nephrotoxicity

Levofloxacin

Uses: MDR Tuberculosis, General antibiotic (Ch 33.1)

MoA: Macrolide antibiotic, Bactericidal

Dose:
- Treatment: PO 10–15 mg/kg/d q24hr (15–20 mg/kg/d q24hr < 5 yrs)
- Prevention (MDR-TB): PO 15–20 mg/kg/d q24hr

AE: Arthropathy, damage to growing cartilage

Linezolid

Uses: MDR Tuberculosis, General antibiotic (Ch 33.1)

MoA: Antibiotic -inhibits bacterial protein synthesis

Dose: PO 15 mg/kg/d q24hr (10–12 mg/kg/d q24hr <6 years)

AE: GIT disturbances, Thrombocytopenia.

Meropenem

Uses: MDR Tuberculosis, General antibiotic (Ch 33.1)

MoA: Antibiotic - inhibits cell wall synthesis

Dose: IV 60–180 mg/kg/d q8hr

AE: Hypersensitivity, GIT upset, Seizures.

Moxifloxacin

Uses: MDR Tuberculosis, General antibiotics (Ch 33.1)

MoA: Antibiotic-Bactericidal

Dose:
- General: PO 7.5–10 mg/kg/d q24hr
- High dose: 10–15 mg/kg/d q24hr

AE: Arthropathy, damage to growing cartilage

Para Amino Salicyclic Acid (PAS)

Uses: MDR Tuberculosis

MoA: Bacteriostatic, PABA antagonist

Dose: PO 200–300 mg/kg/d q12hr (Not for use < 30 kg)

AE: GIT Upset, Liver dysfunction, Hypothyroidism

Pyrazinamide (PZA)

Uses: Tuberculosis treatment (First-line and MDR)

MoA: Bactericidal

Dose: PO 35 (30–40) mg/kg/d q24hr (max 2000 mg/d)

AE: Hepatotoxicity, Photosensitive rash, Lupus-like syndrome

Rifampicin

Uses: Tuberculosis treatment and Prevention, Leprosy, Brucellosis, Meningococcal prophylaxis

MoA: Bactericidal

Dose: As per indications:
- TB treatment: PO 15 (10–20) mg/kg/d q24hr* (max 600mg/d)
- TPT (H-resistant) PO 15 (10–20) mg/kg/d q24hr (4 months)
- Leprosy: PO 10 mg/kg/month (max 450 mg)
- Brucellosis: PO 15–20 mg/kg/d q24hr
- Meningococcal prophylaxis: PO 20 mg/kg/d q12hr × 2 days

AE: Hepatotoxicity, Flu-like illnes

**To be given before breakfast. Red-discoloration of urine and other body secretions is normal after drug-ingestion due to its excretion.*

Streptomycin

Uses: Tuberculosis, Brucellosis, Plague

MoA: Bactericidal

Dose:
- Tuberculosis: IM 15–20 mg/kg/d q24hr (Max 1 gm/d).
- Brucellosis: IM 15–30 mg/kg/d q24hr

AE: Vestibular dysfunction, Nephrotoxicity, Muscle weakness

33.3 ANTI-VIRAL AGENTS

Antiviral agents include *antiretroviral agents* against HIV/AIDS (Ch 10.28) and *non-antiretroviral agents* for other viral infections, discussed in this section.

Common non-antiretroviral agents include: (a) *Nucleoside analogues* - competitive inhibitors of viral DNA polymerase, e.g. acyclovir, (b) *Phosphate analogues* - non-competitive inhibitors of DNA polymerase, e.g. Foscarnet, (c) *Tricyclic amines* - inhibitors of viral replications, e.g. amantidine, (d) *Neuraminidase inhibitors* – blocking the release of virus from infected cells, e.g. oseltamivir, and (e) *Interferons* to inhibit cellular penetration, intracellular assembly and release of viruses from infected cells.

Acyclovir

Uses: Varicella-Zoster, Herpes Simplex, CMV Prophylaxis

MoA: Competitive inhibition of viral DNA polymerase.

Dose: As per indication and mode of administration:
- HSV Encephalitis: IV 20 mg/kg/d q8hr
- Varicella Zoster: PO 20 mg/kg/d q6hr (max 800 mg/d)

AE: Rash, bone marrow suppression, seizures.

Amantadine

Uses: Prophylaxis or treatment of Influenza A.

MoA: Inhibition of viral replication.

Dose: PO 2–4 mg/kg/d q12hr. (max 200 mg/d)

AE: Dizziness, Hypotension, Urinary retention.

Entecavir

Uses: Chronic HBV infection > 2 years of age

MoA: Nucleoside analog - inhibits viral replication.

Doses: PO 0.15–0.5 mg/d q24hr (As per wt bands)

AE: Myalgia, Lactic acidosis

**Use double dose if previously exposed to Lamivudine*

Foscarnet

Uses: Resistant CMV,VCZ, HSV

MoA: Non-competitive inhibition of DNA polymerase.

Dose: As per indications:
- *CMV:* IV 60 mg/kg/dose q8hr (slow, diluted as 12 mg/ml) followed by 90 mg/kg/dose q24hr
- *HSV/VCZ:* IV 120 mg/kg/d q8–12hr.

AE: Seizures, Neuropathy, Nephrotoxicity.

C/I: Renal disease, safety not established in children

Ganciclovir

Uses: CMV

MoA: Competitive inhibition of DNA polymerase.

Dose: Induction IV 10 mg/kg/d q12hr × 1–3 wks, then … Maintenance : IV 5 mg/kg/d q24hr

AE: Rash, Vomiting, Myelosuppression

Peginterferon: Interferons include many non-specific regulatory proteins with antiviral and immuno-modulatory properties, secreted by virus infected leukocytes and fibroblasts. Presently, only Peginterferon α–2a and β-2a are is used in children.

Uses: Chronic HBV and HCV infections

MoA: No direct antiviral activity, induces production of many effector proteins and modify immune response.

Dose: As per product and indications

PegInterferon α-2a:
- Chronic HBV: SC 180 µg/1.73m^2/wk × 48 wks (> 3 yr)
- Chronic HCV: SC 180 µg/1.73m^2/wk × 24–48 wks (> 5 yr)

PegInterferon β-2a:
- Chronic HCV: SC 60 µg/m^2/wk (> 3 yr)

AE: Influenza-like illness, neuropsychiatric complications, bone marrow depression (doses need modification in Neutropenia/Thrombocytopenia.

Isoprinosine

Use: Subacute Sclerosing Panencephalitis (SSPE)

MoA: Uncertain

Dose: PO 50–100 mg/kg/d q12hr

AE: Hyperuricemia, Rash, Arthalgia

Oseltamivir

Uses: Influenza (category B and C disease)

MoA: Neuraminidase inhibitor- blocks release of virus from infected cells.

Dose: As per age/wt , twice a day doses as follows, for 5 days:
- *Infants:* 12 mg (< 3 mo), 20 mg (3–5 mo), 25 mg (6–11 mo)
- *Post-infancy:* 30 mg (<15 kg), 45 mg (15–23 kg), 60 mg (24–40 kg), 75 mg (>40 kg)

**Same dose, but once a day for 10 days is used for prophylaxis in high-risk cases.*

AE: Insomnia, rapid development of resistance.

Ribavarin

Uses: Respiratory syncytial virus (RSV) infections in high-risk cases.

MoA: Competitive inhibitors of viral DNA polymerase.

Dose: PO: 10 mg/kg/d q6–8hr (max 150 mg/d)*

AE: Rash, Hypotension, Seizures.

**Aerosol therapy is preferred but not available in India*

Rimantidine

Uses: Influenza A (in children, for prophylaxis only).

MoA: Inhibition of viral replication.

Dose: PO 5 mg/kg/d q12hr (max 150 mg/d).

AE: Dizziness, Hypotension, Urinary retention.

Valacyclovir

Uses: Varicella in children > 2 yr

MoA: Pro-drug, converts to Acyclovir

Dose:
- Varicella: PO 20 mg/kg/dose q8hr (> 2 yr)
- H. labialis: PO 2 gm/dose q12hr × 1 d (>12 yr)

AE: Headache, Neutropenia, Rash

Valganciclovir

Uses: CMV prophylaxis in transplant cases.

MoA: Pro-drug, converts to Ganciclovir.

Dose: PO 450 mg/m^2/d (Max 900 mg/d)

(*Or* 7 × surface area × creatinine clearance ml/min)

AE: GIT upset, Myelosuppression, Peripheral neuropathy.

Vidarabine (Ara-A)

Use: Herpes Simplex, Varicella Zoster.

MoA: Competitive inhibitors of viral DNA polymerase.

Dose: IV 10–15 mg/kg/d (slowly over 12 hr) q24hr.

AE: Marrow suppression, Neurotoxicity.

33.4 ANTI-FUNGAL AGENTS

Antifungal agents include drugs used for: (a) systemic or invasive fungal infections, and (b) superficial fungal infections, apart from preparations for topical use. Only those drugs, which are used orally/parenterally are listed here, excluding topical preparations.

Amphotericin B

Uses: Systemic fungal infections

MoA: Binds ergosterol to increase fungal cell permeability

Dose: IV 0.25–1.0 mg/kg/d q24hr in DW5% over 6 hr*

(Max 35 mg/kg over 4–6 weeks).

AE: Nephrotoxicity, Hypotension, Fever with chills

Liposomal Amphotericin is less nephrotoxic and preferred with higher doses, i.e. IV 2.5–5.0 mg/kg/d q24hrs in DW 5% over 2 hrs.

**Protect infusion from light*

Caspofungin

Use: Systemic fungal infections

MoA: Echinocandin -disrupts fungal cell wall

Dose: IV 70mg/m^2 (L) > 50 mg/m^2 q24hr (max 70 mg/d)

AE: Edema, Flushing, Headache, Dry mouth

Fluconazole

Uses: Systemic fungal infections

MoA: Increases fungal cell permeability

Dose: IV/PO 12 mg/kg (L) > 3–6 mg/kg/d q24hr

AE: Rash, Liver dysfunction

Flucytosine

Use: Systemic fungal infections

MoA: Inhibits fugal protein synthesis.

Dose: PO 50–150 mg/kg/d q6–8hr

AE: Rash, confusion, marrow suppression

Note: Resistance develops quickly, Never to be used alone, always with amphotericin

Griseofulvin

Use: Superficial (skin/hair/nail) fungal infections

MoA: inhibits fungal replication

Dose: PO 10 mg/kg/d q12–24hr

AE: Photosensitive rash, Diarrhea

Itraconazole

Use: Treatment and prophylaxis of systemic fungal infections

MoA: Increases fungal cell permeability

Dose: PO 3–5 mg/kg/d q24hr (max 400 mg/d)

AE: Rash, Hearing loss, Hepatic/cardiac dysfunction

Ketoconazole

Use: Systemic fungal infections

MoA: Increases fungal cell permeability

Dose: PO 3–6 mg/kg/d q24hr (max 800 mg/day)

AE: Dizziness, Thrombocytopenia, Gynecomastia

Nystatin

Use: Mucocutanous candidiasis, candidal diarrhea.

Dose: PO 1–2 million U/day q6hr

AE: Nil

Note: *For topical use, dissolve as 1 Lac U/ml of glycerine.*

Terbinafine

Use: Superficial fungal infections

MoA: Increases fungal cell wall permeability

Dose: PO 62.5 mg/d q24hr (<20 kg)/ 125 mg/d (>20kg)

AE: None significant

Voriconazole

Use: Systemic fungal infections.

MoA: Increases fungal cell permeability.

Dose: IV/PO 6–9 mg/kg/dose at 0 and12 hr, then 4 mg/kg/d q12hr

AE: Photophobia, Flu-like illness, Liver dysfunction

33.5 ANTI-MALARIAL AGENTS

No single antimalarial agent is effective against all stages of parasite. Current drugs may be divided into:

a. *Drugs acting on hepatic phase (Tissue Schizonticidals),* which destroy the sporozoites, prevent hepatic schizogony or prevent erythrocyte invasion by merozoites. These drugs are used for *chemoprophylaxis* or *radical cure* in Pv malaria.

b. *Drugs acting on erythrocytic phase (RBC Schizonticidal),* which inhibit erythrocytic schizogony and rupture of infected RBCs. These drugs are used for treatment of

malaria, but do not prevent relapse in Pv malaria due to limited action on hepatic phase.

c. *Gametocidal drugs*, which destroy gametes to prevent transmission in new vectors.

d. *Sporonticidal drugs* prevent maturation of parasite within the mosquito to break transmission cycle.

Artemesinin combination therapy **(ACT)** includes use of two or more schizontocidal drugs with different actions. One of these drug is a rapid-acting artemisinin derivative, e.g. artesunate or artemether combined with another slow-acting antimalarials, e.g. lumefantrine or sulfadoxine-pyrimethamine (SP), to prevent emergence of drug resistance. Five ACT combinations are approved by WHO for use in children - Artesunate+Sulfadoxine-Pyrimethamine (ASP), Artemether+Lumefantrine (AL), Artesunate+Amodiaquine (AA), Artesunate+mefloquine (AM), and Dihydroartemisinin+Piperaquine (DHP); of which only first two combinations are used in Indian children.

Artemether with Lumefantrine (AL)*

Uses: Chloroquine-resistant P. falciparum malaria

MoA: Mainly acts on erythrocytic phase, some action on hepatic phase. Gametocidal.

Dose: (based on Artemether):

- *PO*: 20 mg BD (5–14 kg), 40 mg BD (15–24 kg), 60 mg BD (25–34 kg), 80 mg BD (>34 kg) × 3 days
- *IV/IM*: 3.2 mg/kg (L) > 1.6 mg/kg/d q24hr, till possible to switch on full oral treatment as above.

AE: GIT upset, Heart block. Avoid in cases with prolonged QTc interval

**Available as fixed drug combnination (1:6 ratio)*

Artesunate with Sulfadoxine-Pyrimethamine (ASP)*

Uses: Chloroquine-resistant P. falciparum malaria.

MoA: Mainly acts on erythrocytic phase, some action on hepatic phase. Gametocidal.

Dose: (based on Artesunate):

- *Falciparum/Mixed malaria*: PO: 4 mg/kg × 3 days (with SD Sulfadoxine-Pyrimethamine 25/1.25 mg* on day 1 only).
- *Severe malaria*: IV 2.4 mg/kg/d at 0, 12, 24 hrs, then q24hr, till oral treatment is possible with area-specific ACT

AE: None significant, rarely Hemolysis.

**Supplied separately, no fixed drug combination available.*

Chloroquine

Use: Treatment of vivax malaria, chemosuppression of Malaria, Extraintestinal amebiasis, Juvenile rheumatoid arthritis.

MoA: Malaria - mainly acts on erythrocytic phase, limited action on hepatic phase, not gametocidal.

Dose: As per indications:

- *Vivax malaria:* PO 10 mg/kg > 5 mg/kg at 6, 24, 48 hr (4 doses) ***or***
- PO 10 mg/kg at 0 and 24 hr > 5 mg/kg at 48 hrs (3 doses)
- *Malaria chemosuppression:* PO 5 mg/kg/week.
- *Extraintestinal amebiasis:* PO 10 mg/kg/d q8hr × 10 days (max 300 mg/d).

AE: Gastritis, Psychosis, Peripheral neuropathy, Tinnitus.

**may also be given IV, but no longer recommended due to serious side effects.*

Primaquine

Use: Radical cure in P.Vivax malaria, to eliminate gametocytes in *P. falciparum* malaria.

MoA: Mainly acts on hepatic phase, Limited action on erythrocytic phase, Gametocidal.

Dose: As per indications:

- *Radical cure in PV:* PO 0.25 mg/kg/d q24hr × 14 days.
- *Gametocidal in PF:* PO 0.75 mg/kg single dose.

AE: Hemolysis in G6PD deficiency, Methemoglobinemia.

**Not to be used in infants, pregnancy, G6PD deficiency*

Quinine

Use: *Severe* malaria

MoA: Malaria - mainly acts on erythrocytic phase, limited action on hepatic phase, Gametocidal.

Dose: IV 20 mg/kg (L) > IV/PO 10 mg/kg/d 8 hourly × 7 days; with

PO Doxycycline 100 mg/dose q24hr (> 8 yr) or

PO Clindamycin 10 mg/kg/d q12hr (<8 yr).

AE: Hemolysis in G6PD deficiency, hypoglycemia, GIT upset, cinchonism (tinnitus) on long use.

**dilute in 5% DW (2 mg/ml) and infuse slowly over 2–4 hours; No IV Loading dose, if received in last 12 hrs.*

****Note:*** No longer used for oral antimalarial therapy, extraintestinal amebiasis or Rheumatoid arthritis

33.6 ANTI-PROTOZOAL AND ANTI-PARASITIC AGENTS

Albendazole

Uses: Broad spectrum Antihelminth, Neurocysticercosis.

MoA: Blocks glucose uptake by parasite.

Dose: as per indications:

- *General:* PO 400 mg Single dose (200 mg >2 yr)
- *Strongyloides/Tapeworm*: PO 400 mg q24hr × 3 days (200 mg < 2 yr)
- *Giardiasis/ Trichinosis*: PO 400 mg q24hr × 5 days (200 mg < 2 yr)
- *Hydatid cyst*: 400 mg q12hr × 28 days (repeat every 2 weeks for 3 cycles)
- *Neurocysticercosis*: PO 15 mg/kg/d q12hr × 10–14 days

AE: Well tolerated.

Diethylcarbamazine

Uses: Filaria, Tropical pulmonary eosinophilia (TPE), Loeffler's syndrome.

MoA: ? sensitizes microfilaria for phagocytosis.

Dose: As per indication:
- *Filaria/TPE:* PO 6 mg/kg/d q8hr × 21 days
- *Loeffler's syndrome:* PO 15 mg/kg/d q24hr × 4 days

AE: GIT upset, Drowsiness.

Diloxanide Fuorate

Uses: Intestinal amebiasis

MoA: Direct amebicidal.

Dose: PO 20 mg/kg/d q8hr × 7–10 days.

AE: GIT upset, Rash.

Ivermectin

Uses: Onchocerciasis (drug of choice), Broad-spectrum antihelminth, scabies, head lice.

MoA: GABA agonist - Neuroparalysis of parasite.

Dose: as per indications (Avoid < 3 yr/15kg)
- General: PO 150 µg/kg Single dose
- Strongyloidiasis: PO 150 µg/kg × 2 days

AE: Allergic rash, Arthralgia.

Levamisole

Uses: Anti-helminth, immunomodulator e.g. in Nephrotic syndrome

MoA: Spastic paralysis of worms, Immunomodulant.

Dose: As per indications:
- *Ascariasis:* PO 2 mg/kg single dose.
- *Hookworm :* PO 50 mg q6hr × 2–3 days.
- *Immunomodulator :* PO 2 mg/kg/dose Alt.day.

AE: GIT upset, Drowsiness.

Mebendazole

Use: Broad-spectrum antihelminth.

MoA: Blocks glucose uptake by parasite.

Dose: As per indications:
- *General:* PO 100 mg/dose q12hr × 3 days (Single dose for Enterobiasis)
- Hydatid cyst: 30 mg/kg/d q8hr × 4 weeks

AE: well tolerated. (Not recommended < 2 yr)

Metronidazole

Uses: Amebiasis, Giardiasis, Trichominiasis, Anerobic infections.

MoA: Intermediate metabolites lethal to pathogen DNA.

Dose: As per indications:
- Anerobic inf: IV/PO 30–40 mg/kg/d q6–8hr
- Amebiasis: IV/PO 30–50 mg/kg/d q6–8hr
- Others: 10–30 mg/kg/d q8hr

Caution: Infuse IV dose slowly over 30–60 minutes.

AE: Metallic taste, Nausea, Dizziness, Peripheral neuropathy.

**Ineffective in asymptomatic cyst passers and chronic intestinal amebiasis.*

Miltefosine

Uses: Kala azar

MoA: Protein kinase B inhibition

Dose: PO 2.5 mg/kg/d q24hr × 28 days

AE: Rash, GIT upset. Not to use < 2 yrs.

Nitazoxanide

Uses: Amoebiasis, giardiasis, cryptosporidium, antihelminth.

MoA: Interferes with anerobic metabolism of parasite.

Dose: As per age:
- 3 yr: PO 100 mg/dose q12hr × 3 days
- 4–11 yr: PO 200 mg/dose q12hr × 3 days
- >12 yr: PO 500 mg/dose q12hr × 3 days

AE: Gastric upset, Rash, Abdominal pain.

Niclosamide

Uses: Intestinal tapeworm infestation.

MoA: Wormicidal, inhibits anerobic metabolism.

Dose: As per indications:
- General: Single dose PO 500 mg (<2 yr), 1 gm (2–6 yr), 2 gm (> 6 yr)
- *H. nana:* Single dose as above on Day 1, then half the dose q24hr × 6 days
- Give a purgative after 2 hr to flush worms

AE: Dizziness, rash, GIT upset.

Ornidazole

Uses: Amebiasis, Giardiasis.

MoA: Intermediate metabolites lethal to pathogen DNA.

Dose: PO 30–40 mg/kg/d q24hr × 3 days

AE: Metallic taste, Nausea, Dizziness

Paromomycin

Uses: Second-line drug in Amebiasis, Giardiasis, Cryptosporidium, Kala-azar.

MoA: Non-absorbable aminoglycoside

Dose: PO 25–35 mg/kg/d q8hr × 7 days.

AE: Vestibulocochlear toxicity, Nephrotoxicity.

Piperazine Citrate

Uses: Ascariasis, enterobiasis.

MoA: Flaccid paralysis of worms.

Dose: As per indications - (rarely used at present)

- Ascariasis: 75 mg/kg/d q24hr × 2 days
- Enterobiasis: 65 mg/kg/d q24hr × 7 days

AE: Neuropsychiatric or extrapyramidal reactions.

C/I in epilepsy.

Pyrantal Palmoate

Uses: Broad-spectrum antihelminth.

MoA: Spastic paralysis of worms.

Dose: PO 11 mg/kg/dose, as follows:

- *General:* Single dose
- *Hookworm:* Repeat q24hr × 3 days
- *Pinworm:* Repeat Single dose after 2 weeks.

AE: Well tolerated. Avoid in hepatic dysfunction.

Praziquantel

Uses: NCC, Tapeworms, Trematodes, Schistosomiasis.

MoA: ? Spastic paralysis of intestinal worms.

Dose: As per indications:

- *NCC:* PO 50 mg/kg/d q8hr × 10–14 days.
- *Tapeworm*: PO 10–20 mg/kg single dose
- *Trematodes:* PO 75 mg/kg/d q8h × 2 days
- *Schistosomiasis:* PO 60 mg/kg/d q8hr × 11–2 days.

AE: CNS depression, Rash.

Pyrimethamine- Sulfadoxine

Use: Toxoplasmosis prophylaxis and treatment, Falciparum malaria (with artesunate)

MoA: Folate antagonist, In malaria - mainly acts on hepatic phase, gametocidal, sponrontidical.

Dose: As per indications:

- *Toxoplasma prophylaxis (+ dapsone):* PO 1 mg/kg/d.

Toxoplasma treatment (+sulpha):
PO 2 mg/kg/d q12hr × 3 days, then-
PO 1 mg/kg/d q24hr × 6 months.

- *Falciparum malaria (with Artesunate only)*
PO 25/1.25 mg/kg single dose.

AE: Megalobastic anemia, photosensitive rash.

Note: Add Folinic acid PO 5 mg/kg alternate day in cases on prolonged therapy, to avoid megaloblastic anemia.

Thiabendazole

Uses: Stronglydosis, cutaneous/visceral larva migrans, trichinosis

MoA: inhibits helminth-specific enzyme fumarate reductase.

Dose: PO 50 mg/kg/d q12hr × 2–5 days

AE: Dizziness, GIT upset

Tinidazole

Uses: Amebiasis, Giardiasis.

MoA: Intermediate metabolites lethal to pathogen DNA.

Dose: PO 50 mg/kg/d q24hr × 3 days (Single dose for Giardiasis)

AE: Metallic taste, nausea, dizziness

33.7 GENERAL MEDICATIONS

Acetazolamide

Uses: Cerebral edema (raised ICP), Glaucoma

MoA: Carbonic anhydrase inhibitor – reduces production of CSF/aqueous humor.

Dose: As per indications:

- Cerebral edema: PO 25–100 mg/kg/d q6–12hr
- Others: PO 8–30 mg/kg/d q8–12hr

AE: Metabolic acidosis, Hypochloremia, Hypokalemia

**Avoid in liver/renal failure*

Acetylcysteine

Uses: Paracetamol poisoning, Chronic lung disease, Meconium ileus

MoA: Blocks toxic metabolite of paracetamol, Mucolytic agent

Dose: As per indications:

- *Paracetamol antidote*:
  IV/PO 140 mg/kg (L) > 70 mg/kg/dose q4hr ***or***
  IV 150 mg/kg in 1 hr > 50 mg/kg in 4 hr > 100 mg/kg in 16 hr
  (Each dose dissolved in 100–500 ml of DW5%)
- *Mucolytic:* Nebulization 6–10 ml q6–8hr (10% sol)
- Meconium ileus: PR 5–10 ml/kg (10% sol) q6hr

AE: Stomatitis, GIT upset, Urticaria

Acetylsalicylic Acid (Aspirin)

Uses: NSAID, Rheumatic fever, Kawasaki disease, Thrombotic disorders.

MoA: Prostaglandin synthesis inhibitor – Anti-inflammatory, anti-platelet activity.

Dose: As per indications:

- *Rheumatic fever*: PO 50–70 mg/kg/d q6hr × 3–5 d > 50 mg/kg/d q6hr × 3 wk > 25 mg/kg/d q6hr x4–6 wk.
- *Kawasaki disease*: PO 80–100 mg/kg/d q6hr till afebrile for 48 hrs > 3–5 mg/kg/d q12–24hr
- *Thromboembolic disorders*: PO 3–5 mg/kg/d q12–24hr
- *General NSAID*: PO 10–15 mg/kg/d (*rarely used in children*)

A/E: Gastritis, Bronchospasm, Tinnitus, Reye syndrome*

**Avoid in viral illness due to potential risk of Reye syndrome.*

Activated Charcoal

Uses: Gut decontamination in poisoning

MoA: Luminal adsorbent

Dose: PO 1–2 gm/kg* with 1–2 hr of poison ingestion, repeat if required.

AE: Constipation, Black stools

**As slurry or crushed tablets, with a cathartic. Repeat if required.*

ACTH (Adrenocorticotropic Hormone)

Uses: Infantile spasms, Myasthenia gravis, ACTH stimulation test

MoA: Stimulates adrenal cortex to release steroids.

Dose: As per indications:

- *Infantile spasms*: SC/PO 20–40 U/kg q24hr × 2–6 weeks.
- *Others*: IV/IM/SC/PO 1.6 U/kg/d q6–8hr.

AE: Cushingoid features, hyperglycemia, hypertension.

Adenosine

Uses: Supraventricular tachycardia

MoA: Slows AV nodal conduction

Dose: IV 0.1mg/kg/dose (Max 6 mg), repeat every 2 minutes with increasing dose by 0.1 mg/kg till response (max 0.3 mg/kg/dose). Push rapidly and flush with 10 ml saline.

AE: Heart blocks, Flushing, Bronchospasm.

Adrenaline (Epinephrine)

Uses: Cardiac arrest, Anaphylaxis, Shock, Acute asthma.

MoA: α and β adrenergic agonist (inotrope and vasoconstrictor).

Dose: As per indications:

Resuscitation:

- IV 0.1 ml/kg (1:10000) q3–5 min , if required; or
- IT 0.1 ml/kg/dose (1:1000)
- *Circulatory Shock*: IV 0.1–0.5 µg/kg/min
- *Anaphylaxis*: SC 0.01 ml/kg (1:1000), repeat after 15 min, if required
- *Acute asthma* : SC 0.01 ml/kg/dose (1:1000 sol)
- *Croup/bronchiolitis*: Nebulization 0.5 ml/kg/dose (1:1000 sol) in 3 ml NS.

AE: Tachycardia, Hypertension, CNS excitation.

Albumin (20%)

Use: Hypoproteinemia, Hypovolemic shock.

MoA: Colloidal plasma volume expander .

Dose: IV 0.5–1.0 gm/kg/dose (slowly over 1–2 hour).

AE: Volume overload, pulmonary edema, Allergy

Allopurinol

Uses: Treatment and prevention of hyperuricemia (Gout)

MoA: Xanthine-oxidase inhibitor.

Dose: IV/PO 10 mg/kg/d q8hr (Max 800mg/d).

(Dilute IV dose as 6 mg/ml and infuse slowly in 30 min)

AE: Rash, Vasculitis, Nephrotoxicity, Neuropathy.

Alprazolam

Uses: Anxiety disorders, General sedative

MoA: Benzodiazepine- potentiates neuroinhibitory GABA action

Dose: PO 0.005–0.02 mg/kg/dose q8hr

AE: Sedation, Withdrawal seizures

Alprostadil (Prostaglandin E_1)

Use: To maintain patency of ductus arteriosus in cyanotic CHDs.

MoA: Peripheral Vasodilator, inhibits platelet aggregation

Dose: IV 0.005–0.01 µg/kg/min, titrate to response

AE: Hypotension, Apnea, Gastric outlet obstruction.

Aluminum Magnesium Hydroxide

Use: Prevention/treatment of acute gastritis.

MoA: Antacid - Gastric acid neutralizer.

Dose: PO 5–10 ml/dose q6hr

AE: Diarrhea (Magnesium salts), Constipation (Aluminum salts).

*Many antacids contain combination of both salts.

Aminocaproic Acid

Use: Hemorrhagic disorders, sp. those with hyperfibrinolysis.

MoA: Hemostatic agent - Plasminogen inhibitor

Dose: PO/IV 100 mg/kg q6hr.

AE: Hypotension, nasal stuffiness.

Avoid in DIC and hematuria. Monitor D-dimer assay.

Aminophylline

Uses: Status asthmatics, Left ventricular failure

MoA: Converts to Theophylline in body – a Phosphodiasterase inhibitor, relaxing smooth muscles in bronchi and pulmonary vessels

Dose: IV 5–6 mg/kg (L*) > 1 mg/kg/hr.

*(*Dilute 10 times in Normal saline and infuse in 20–30 min)*

AE: Arrhythmia, Tremors, Ataxia, worsens GERD.

**Low safety margin. To avoid toxicity - (a) monitor plasma drug levels (N: 5–15 µg/ml). (b) No loading dose, if received aminophylline in past 72 hours.*

Amiodarone

Use: Refractory arrhythmia

MoA: Sodium channel inhibitor, prolongs repolarization

Dose: As per route of administration:

- IV 2–5 mg/kg (L in 30–60 min) >5–15 µg/kg/min
- PO 5–15 mg/kg/d q12–24hr

AE: Proarrhythmia, Rash, Pulmonary fibrosis, Hypothyroidism

**Contraindicated in sick sinus disease/AV block without pacemaker*

Amiloride

Uses: Hypertension, Fluid overload

MoA: Aldosterone antagonist (Potassium-sparing diuretic)

Dose: PO 0.4–0.6 mg/kg/d q12–24hr (Max 20 mg/d)

AE: Hyperkalemia*

**Never used alone, used with thiazide diuretics*

Amitriptyline

Uses: Antidepressant, Migraine prophylaxis

MoA: Increases synaptic serotonin levels

Dose: PO 1.0–1.5 mg/kg/d q 12–24 hr (Not to use <12 yr)

AE: Sedation, Hypotension, Dry mouth, Weight gain.

Amlodipine

Uses: Hypertension

MoA: Calcium channel blocker

Dose: PO 0.1–0.2 mg/kg/d q24hr (max 0.6mg/kg)

AE: Edema, Dizziness, Headache, Palpitation

Ammonium Chloride

Uses: Metabolic alkalosis, Poisoning (urinary acidification to enhance urinary excretion).

MoA: Systemic/urinary acidification by exchange of bicarbonate ions with chloride ions.

Dose: IV/PO 75 mg/kg/d q6hr

AE: Hyperchloremia, Hyperkalemia, Hyperammonemia.

Amrinone

Uses: Low-output CCF/Shock, as adjuvant

MoA: Phosphodiesterase inhibitor (Inotrope, Vasodilator).

Dose: IV 0.75 mg/kg (bolus) > 5–10 µg/kg/min (max 10 mg/d)*

AE: Hypotension, Arrhythmia, Thrombocytopenia

Contraindicated in Cardiomyopathy.

**Do not use dextrose for infusion. Protect infusate from light.*

Anti-Diphtheria Serum (ADS) or Diphtheria Antitoxin

Uses: Treatment of Diphtheria

MoA: Neutralization of diphtheria toxin

Dose: Depends on severity and duration of disease:

- *Pharyngeal/laryngeal <48 hr:* IV 20,000–40,000 IU
- *Nasopharyngeal:* IV 40,000–60,000 IU
- *Severe airway obstruction >48 hr:* IV 80,000–1,20,000 IU.

AE: Anaphylaxis, Serum sickness, Coaguloapthy

**Contraindicated in IgA deficiency.*

**intradermal sensitivity test required before infusion.*

Anti Rh-D Immunoglobulins

Uses: Prevention of Rh-HDN, Treatment of ITP

MoA: (a) *For Rh-HDN* - bind Rh+ve fetal RBCs in maternal circulation and eliminate them before stimulation of specific antibody response, (b) *For ITP* - bind Rh+ve RBCs of the patient producing mild hemolysis. These sensitized RBCs are cleared preferentially in spleen then platelets, thus reducing platelet destruction (works only in Rh+ve ITP patients)

Dose: As per indications:

- *Rh-HDN:* IM 300 µg* to mother within 72 hr of delivery
- *ITP:* IV 50–75 µg/kg Single dose

AE: None, Mild anemia

**Use double dose in twin pregnancy*

Anti-Snake venom (ASV)

Uses: Poisonous snake-bite

MoA: Neutralization of venom (Polyvalent ASV against Cobra, Krait, Russel viper and saw-scaled viper)

Dose: As per the type of snake-bite:

- *Neuroparalytic*: IV 100 ml stat in 30 min > 100 ml after 1 hr if no improvement (max 200 ml).
- *Vasculotoxic*: IV 100 ml stat in 30 min > 60 ml every 6 hr till normalization of clotting time (max 300 ml)

*dilute in 5–10 ml/kg normal saline and infuse @1–2 ml/min

AE: Anaphylaxis, serum sickness.

- *No test dose is required* considering risk-benefit ratio, but cases with history of animal serum allergy or strong atopy should be given ASV only if symptomatic.
- *Prophylactic Epinephrine* 0.005 mg/kg may be given at the beginning of infusion or must be kept ready during infusion.

Astemizole

Uses: Allergic conditions (not <6 yr age)

MoA: Antihistamine-H_1 receptor antagonist

Dose: PO 0.2 mg/kg/d q24hr

AE: Sedation, Syncope, Arrhythmia

Atenelol

Uses: Hypertension, Arrhythmia, Thyrotoxicosis, Migraine prophylaxis

MoA: Selective β_1 adrenergic blocker

Dose: PO 0.8– 2.0 mg/kg/d q12hr

AE: Bronchospasm, Heart blocks, Constipation

C/I in cardiogenic shock/pulmonary edema

Atomoxetine Hydrochloride

Uses: Attention deficit-hyperactivity disorder

MoA: Norepinephrine transport inhibitor

Dose: Start with PO 0.5 mg/kg/d q24hr × 3 days > titrate up gradually to max 1.2 mg/kg/d

AE: Headache, Insomnia, Vomiting

Atorvastatin

Uses: Severe Familial hypercholesterolemia

MoA: HMG-CoA reductase enzyme inhibitor

Dose: PO 10–20 mg/d q24hr (Not to use < 6 yr).

AE: Dyspepsia, Pancreatitis, Hepatitis

Atropine

Uses: Resuscitation, Organophosphorus (OP) poisoning, Pre-operative vagolysis

MoA: Anticholinergic agent

Dose: As per indication:

- *Resuscitation*: IV/IT 0.01–0.02 mg/kg/dose, repeat every 5 min (Max 1 mg)
- *Pre-operative*: IV 0.01 mg/kg/dose (30 min before procedure)
- *OP poisoning*: IV 0.02–0.05 mg/kg/dose, repeat every 10–15 min till full mydriasis

AE: Dry mouth, Blurred vision, Palpitation

Azathioprine

Uses: Immunosuppressant in—(a) Refractory immune disorders, e.g. SLE, JRA, nephrotic syndrome, (b) organ/marrow transplant to prevent graft rejection.

MoA: Inhibits nucleic acid synthesis (purine metabolism).

Dose: PO 1 mg/kg/d × 6–8 weeks.

AE: Gastric upset, Rash, blood dyscrasia, hepatotoxic, Lymphoma on prolonged use.

Baclofen

Uses: Skeletal muscle relaxant in cerebral palsy and other spastic disorders

MoA: Inhibits spinal synaptic transmission

Dose: PO 1–2 mg/kg/d q6–8hr (max 40 mg/d).

AE: Sedation, Ataxia, Vertigo, Psychiatric reactions

Beclomethasone

Uses: Asthma – Maintenance, Anti-inflammatory reliever

MoA: Intermediate-acting steroid

Dose: MDI/DPI 200 - >800 µg/d q6–12hr

AE: Oral thrush. may be prevented by gargles after inhalation

Bethanechol

Uses: Non-obstructive urine retention, GERD

MoA: Cholinergic agent

Dose: PO 0.3–0.6 mg/kg/d q6–8hr.

AE: Hypotension, Diarrhea, Bronchospasm

Biotin

Uses: Biotinidase deficiency or dependency

MoA: Nutritional supplement

Dose: PO/IM 2–5 mg/d q24hr (10 mg/d in dependency)

AE: None.

Bisacodyl

Uses: Constipation, preparation for abdominal X-ray

MoA: Laxative - stimulates intestinal peristalsis

Dose: PO/PR 5–10 mg, as required

AE: Fluid/electrolyte imbalance, Abdominal cramps

Bretylium

Uses: Refractory Ventricular Arrhythmia

MoA: Inhibits release of neurotransmitter, prolongs repolarization and refractory period.

Dose: IV 2–5 mg/kg/dose repeat q20 min till response, then 5–10 mg/kg q6hr

AE: Hypotension, Bradyarrhythmia

Budesonide

Uses: Asthma – Maintenance, anti-inflammatory reliever

MoA: Longer-acting steroid

Dose: As per indication:

- *Asthma:* Nebulization 500–1000 µg/dose q12hr
  MDI/DPI: 100–>800 µg/dose q12hr
  Allergic rhinitis: Intranasal 50–100 µg/dose q12–24hr

AE: Oral/nasal thrush. Oral thrush may be prevented by gargles after inhalation.

Bumetanide

Uses: Moderate/severe edema or fluid overload.

MoA: Loop-diuretics (acts on Loop of Henle).

Dose: PO 0.01–0.1 mg/kg/d q24hr (max 10 mg/d)

AE: Hypokalemia, Muscle cramps, GIT upset

Calcium Carbonate

Uses: Treatment and prevention of calcium deficiency

MoA: Nutritional supplement

Dose: PO calcium 400–1200 mg/d q12–24hr

AE: Constipation, Hypercalcemia, hypercalciuria (renal stones)

Calcium Gluconate 10% (1 ml: 0.45 mEq)

Uses: Hypocalcemic tetany/seizures,

MoA: Correction of hypocalcemia

Dose: IV 1–2 ml/kg/dose over 8–10 min with cardiac monitoring may be repeated q8hr.

AE: Bradycardia, Sudden cardiac arrest, Thrombophlebitis

Caffeine Citrate

Uses: Neonatal apnea

Dose: IV/PO 10–20 mg/kg/d > 5–10 mg q24hr

AE: GIT upset, Irritability, jitteriness, arrhythmia

Captopril

Uses: Hypertension, CCF

MoA: Angiotensin converting enzyme (ACE) inhibitor.

Dose: PO 0.2–0.5 mg/kg q8–12hr (max 6 mg/kg/d)

AE: Proteinuria, Hyperkalemia

Note: Contraindicated in bilateral renal artery stenosis

Carbamazepine

Uses: Epilpesy (Broad spectrum), Psychiatric disorders

MoA: Sodium-channel inhibitor

Dose: PO 10–30 mg/kg/d q8–12hr (start with lower dose)

AE: Ataxia, Drowsiness, Rash, Aplastic anemia

Note: Preferably monitor drug levels (N: 6–12 mg/ml)

Carbimazole (Neomercazole)

Uses: Hyperthyroidism

MoA: Peroxidase inhibitor, blocks thyroxine synthesis.

Dose: PO 0.5–1.0 mg/kg/d q12–24h (Max 30 mg/d)

AE: Urticaria, Blood dyscrasia, Lupus-like syndrome

Note: Carbimazole metabolizes to Methimazole in vivo for action.

Carnitine

Uses: Carnitine deficiency disorders

MoA: Nutritional supplement.

Dose: PO/IV 50 mg/kg/d q6–8hr

AE: Vomiting, Abdominal cramps, Body odor

Note: Avoid in severe renal disease

Carvedilol

Uses: Hypertension, CCF

MoA: Non-selective adrenergic blocker

Dose: PO 0.05–0.35 mg/kg/d q12hr (titrate up slowly)

AE: Dizziness, AV block, arrhythmia

Note: Contraindicated in liver/renal dysfunction

Cetrizine

Uses: Allergic conditions (Not for use <6 mo).

MoA: Long-acting Antihistamine - H_1 receptor antagonist.

Dose: PO 0.2 mg/kg/d q24hr *or*

2.5 mg (6 mo-2yr), 5 mg (2–6 yr),10 mg >6 yr

AE: Mild sedation (less than other antihistamines)

Chloral Hydrate

Uses: Pre-procedure sedation, Anxiety

MoA: Uncertain, due to metabolite Trichloroethanol

Dose:

- *Pre-procedure*: PO 50–75 mg/kg/dose 30 min before procedure
- *Anxiety*: PO 25–50 mg/kg/d q6–8hr

AE: Hepatotoxic on prolonged use

Chlorphenarmine Maleate

Use: Allergic conditions.(Not for use < 2 yr)

MoA: Antihistamine - H_1 receptor antagonist

Dose: PO 0.5.g/kg/d q6hr *or*

PO 4–6 mg/dose q6–8hr (8–12 mg >6 yr)

AE: Sedation, Paradoxical hyperactivity, Dry mouth.

Chlorpromazine

Uses: Psychosis, Chorea, Vomiting

MoA: Antihistamine, also blocks dopaminergic receptors

Dose: As per Indications:

- *General*: PO/IV 2.5–5.0 mg/kg/d q6–8hr (max 80 mg/d)
- *Chorea*: PO 50 mg/d q12–24hr (max 300 mg/d)

AE: Extrapyramidal reactions, Hypotension, Sedation

Chlorothiazide

Uses: Diuretic, Moderate edema/fluid overload.

MoA: Inhibits Na^{+}/Cl^{-} reabsorption at distal tubules.

Dose: As per route of administration:

- PO 20 mg/kg/d q12hr
- IV 4 mg/kg/d q12hr

AE: Hyperglycemia, Blood dyscrasia, Hyperuricemia

Chlorzoxazone

Use: Skeletal muscle relaxant in muscle spasm/pain

MoA: Depresses sub-cortical and spinal reflex activity

Dose: PO 20 mg/kg/d q6–8hr

AE: Drowsiness, Dizziness, Dry mouth

Cholestyramine Resin

Use: Cholestatic jaundice.

MoA: Binds bile salts to form unabsorbable complexes

Dose: PO 240 mg/kg/d q8–12hr (max 8 gm/d)

AE: Hyperchloremic acidosis, Malabsorption

Cimetidine

Uses: Gastroesophageal reflux disease (GERD)

MoA: H_2 receptor antagonist.

Dose: PO 10–20 mg/kg/d q6–12hr

AE: Drowsiness/dizziness

Clobazam

Uses: Epilepsy, Febrile seizure prophylaxis

MoA: Sodium-channel inhibitor.

Dose: As per indications:

- Antiepileptic: PO 0.25–1.0 mg/kg/d q12–24hr.
- Febrile seizure prophylaxis: 0.5 mg/kg/dose q12hr × 48 hr

AE: Drowsiness, Behavioral problems, Weight gain

Clomipramine

Uses: Obsessive-compulsive disorders (Not for use <10 yr)

MoA: Inhibits serotonin re-uptake in brain.

Dose: PO 25–100 mg/d q24hr (start with lower dose).

AE: Sedation, Insomnia, Arrhythmia

Clonazepam

Uses: Epilepsy, Sedation, Anxiety disorders

MoA: Chloride channel blocker.

Dose: PO 0.01–0.03 mg/kg/d q8–12hr (max 0.2 mg/kg/d)

AE: Drowsiness, Behavior problems

Clonidine

Use: Hypertension, Migraine

MoA: α-adrenergic antagonist

Dose: PO 5–7µg/kg/d q6hr (max 25µg/kg/d)

AE: Postural hypotension, Dry mouth, Constipation.

Note: Titrate up the dose slowly, Don't discontinue suddenly, taper over 1–2 weeks

Clorazepate

Uses: Epilepsy (Add-on drug), Anxiety disorders

MoA: Benzodiazepine - potentiates neuroinhibitory GABA action

Dose: PO 7.5–15 mg/d q12hr (titrate up to max 60 mg/d)

AE: Sedation, confusion, blurred vision.

Codeine

Uses: Analgesic, Sedative

MoA: Narcotic (Opioid) analgesic, suppresses cough centers*.

Dose: PO 0.5–1.5 mg/kg/d q6–8hr

AE: Drowsiness, constipation

**not to be used as cough suppressant*

Cromolyn Sodium

Uses: Long-term control in asthma and allergic disorders

MoA: Mast cell stabilizer.

Dose: As per indications:

- *Asthma:* MDI 800–1600 µg/dose q6–8hr.
- *A. Rhinitis*: Nasal spray (40 mg/ml) 1–2 drops q6–8hr.
- *A. conjunctivitis:* Eye drops (4%) 1–2 drops q6–8hr.

AE: Local burning sensation, Reflex cough with MDI.

Cyanocobalamin (Vit B_{12})

Use: Vitamin B_{12} deficiency, Pernicious anemia

MoA: Nutritional supplement

Dose: As per indications:

- *Megaloblastic anemia:* IV/IM/PO* 250–1000 µg q24hr × 2–4 wk, then weekly × 6 mo
- *Neurological complications (Pernicious Anemia*): IV/IM 1000 µg//d × 2 wk, then alternate week × 6 mo, then monthly for life.

AE: None.

**Oral therapy is equally effective, in absence of malbasorption*

Cyclophosphamide

Uses: Leukemia/Lymphoma, Resistant nephrotic syndrome

MoA: Alkylating agent - interferes with DNA function, Immunosuppresant

Dose: As per indications:

- *Neoplasms:* As per protocols.
- *Nephrotic syndrome*: PO 2–3 mg/kg/d (with steroids).

AE: Hemorrhagic cystitis, Cardiotoxicity

Note: Ensure adequate hydration to prevent cystitis may also use Mesna PO/IV 20–40% (w/w) 3 doses at 4-hourly interval, to detoxify urotoxic metabolites.

Cyproheptadine

Use: Allergic conditions. Migraine prophylaxis

MoA: Antihistamine- H_1 receptor antagonist.

Dose: PO 0.25 mg/kg/d q8hr

AE: Sedation, dry mouth, increased appetite*

**Avoid misuse as appetite stimulant*

Cyclosporine

Uses: Immunosuppressant in—(a) Refractory immune disorders, e.g. nephrotic syndrome, (b) Organ/marrow transplant to prevent graft rejection.

MoA: Inhibits production and release of interleukin II and consequent activation of T-lymphocytes.

Dose: Varies with indication. Generally:

IV/PO 2–10 mg/kg/d q12–24hr

AE: Hypertension, Hirsutism, tremors, gingivitis.

Note: Preferably monitor drug levels periodically to avoid toxicity.

Dantrolene

Use: Skeletal muscle relaxant in cerebral palsy and other spastic disorders, malignant hyperthermia.

MoA: Inhibits calcium release from sarcoplasmic reticulum.

Dose: As per indications:

- *Spasticity:* PO/IV 0.5–3.0 mg/kg/dose q12hr
- *Hyperthermia:* PO/IV 1–2 mg/kg/dose q6hr

AE: Drowsiness, Seizures, Gastrointestinal upset

Deferasirox

Use: Prevention of iron overload in Thalassemia

MoA: Oral Iron-chelating agent

Dose: PO 15–30 mg/kg/d q24hr (Max 40 mg/kg)

AE: GIT upset, Skin rash, Renal damage

Note: Disperse the tablet in water before consumption. Don't chew or swallow

Deferiprone

Uses: Prevention of iron overload in Thalassemia

MoA: Oral iron chelating agent

Dose: PO 75–100 mg/kg/d q8–12hr.

AE: Arthropathy. Agranulocytosis

Desferioxamine

Use: Iron poisoning, Prevention of iron overload in thalassemia

MoA: Iron-chelating agent

Dose: As per indication:

- Iron poisoning: IV 15 mg/kg/hr* or 50 mg/kg/dose q6hr
- Thalassemia: SC 20–50 mg/kg/d over 8–12 hr (5–6 nights a week)

AE: Flushing, cramps, hypotension, Hearing loss, cataract

Note: *Continue till the child passing vinrose-color urine (due to iron-desferioxamine complex)*

Desloratadine

Uses: Allergic conditions (Not for use < 6 mo)

MoA: Long-acting Antihistamine- H_1 receptor antagonist.

Dose: PO 1 mg/dose q24hr (2 mg/dose > 5 yr age)

AE: Mild sedation(less than other antihistamines).

Desmopressin (DDAVP)

Uses: Diabetes insipidus, Nocturnal enuresis, Hemostasis during surgery in hemophilia.

MoA: Vasopressin analog. Hormone replacement, peripheral vasoconstriction

Dose: As per indication:

- *D. Insipidus:* Intranasal 5–30 µg q12hr (or PO 0.1–1.2 mg/d q12hr)
- *Nocturnal Enuresis:* PO 0.2–0.6 mg q24hr, 2 hour before bedtime.
- *Hemophilia*: IV 0.3 µg/kg 30 min before surgery (or Intranasal 150 µg 2hr before surgery.

AE: Water intoxication, Hyponatremia

Dexamethasone

Uses: Allergic/inflammatory conditions, Status asthmaticus, Cerebral edema. Congenital adrenal insufficiency (CAH).

MoA: Longer-acting Corticosteroid

Dose: As per indications:

- *General:* IV/IM/PO 0.2–0.5 mg/kg/d q6hr
- *CAH:* 0.5–1.5 mg/d q6–8hr
- *Cerebral edema:* 0.5 mg/kg/dose q6–8hr

AE: Cushingoid appearance, Fluid retention, Hypertension, Hyperglycemia, Immunosuppression, Gastritis, Osteoporosis, Cataracts, Growth Failure.

Dextroamphetamine

Uses: Attention-deficit disorder, Narcolepsy

MoA: Inhibits synaptic reuptake of dopamine

Dose: PO 2.5–5 mg/d q24hr titrate up weekly (max 60 mg/d).

AE: Hypertension, Neuroexcitation, Anorexia, Dependence

Dextran 10%

Uses: Hypovolemic shock, usually in Trauma.

MoA: Colloidal plasma volume expander

Dose: IV 20 ml/kg/d on day 1 >10 ml/kg/d (max 5 days).

AE: Pulmonary edema, bleeding due to platelet dysfunction

Dextromethorphan

Uses: Cough suppressant.

MoA: suppresses medullary cough centers.

Dose: PO 15 mg q12hr (4–6 yr), 30 mg (6–12yr), 60 mg (>12yr)

AE: Drowsiness, constipation.

Diazepam

Uses: Status epilepticus, Pre-procedure sedation, Anxiety disorders, muscle spasms in tetanus.

MoA: Benzodiazepine - potentiates neuroinhibitory GABA action

Dose: As per Indications:

- General: IV/PO/PR 0.2–0.3 mg/kg/dose* q6–8hr
- Tetanus: As above *or* IV 0.05 mg/kg/hr (max 10 mg/kg/d)

AE: Respiratory depression, Drowsiness, Ataxia,

**slowly over 2–3 min. may repeat every 30 min, if required.*

Note: Antidote: see Flumazenil

Diazoxide

Uses: Hypertension, Hyperinsulinemic hypoglycemia

MoA: Direct vasodilator, inhibits insulin-release

Dose: As per indications:

- *Hyperinsulinemia:* PO 8–15 mg/kg/d q8–12hr.
- *Hypertension:* IV 1–5 mg/kg/dose q5–15 min (max 150 mg/dose)

AE: Hypotension, Hyponatremia, Hyperglycemia

Diclofenec

Uses: NSAID, mainly Anti-inflammatory

MoA: Prostaglandin synthesis inhibitor

Dose: PO 1–3 mg/kg/d q8hr

A/E: Gastritis, Nephrotoxicity (avoid in renal disease)

Dicyclomine

Use: Anti-spasmodic (abdominal colic)

MoA: Anti-cholinergic agent

Dose: PO/IM 5–10 mg/dose; repeat q8hr if required

AE: Constipation, palpitation, Dry mouth

Digoxin

Uses: CCF, Supraventricular tachycardia

MoA: Inotrope, slows down AV conduction to reduce heart rate and improve cardiac filling.

Dose: As per age, route of administration and need for rapid/slow digitalization. (See Ch 17.4)

AE: Arrhythmia, Vomiting, Diplopia, Green-vision.

Note: Contraindicated in AV block, constrictive pericarditis, aortic stenosis. Reduce dose in renal impairment.

Note: Digoxin specific fab antibodies are used as antidote in digitalis toxicity with dose as follows:

Dose (in mg): Serum digoxin levels (ng/ml) × wt × 0.425.

Diltiazem

Use: Hypertension, Arrhythmia (Atrial)

MoA: Calcium-channel blocker

Dose: PO 1.5–2.0 mg/kg/d q6–8hr.

AE: Hypotension, Edema, Heart-block

Dimercapol (BAL)

Uses: Lead, Gold, Arsenic and Mercury poisoning

MoA: Chelating agent

Dose: As per indication:

- *Lead poisoning:* IV 75 mg/m^2/dose q4hr
- *Others:* IV 2–4 mg/kg/dose q4–6 hr

AE: Hypertension, Nephrotoxicity

Diphenhydramine

Uses: Antiallergic, Antitussive, Extrapyramidal reactions.

MoA: Antihistamine - H_1 receptor antagonist

Dose: PO 5 mg/kg/d q8hr

AE: Sedation, Dry mouth, Addiction

Disodium Hydrogen Citrate

Uses: Urinary infection (Dysuria), Gout, Renal Stones

MoA: Systemic and urine alkalinizer, contains Sodium 1 mEq, potassium 1 mEq, bicarbonate 2 mEq

Dose: PO 2.5 – 5 ml/dose q6–8hr with water

AE: Hypernatremia/hyperkalemia, alkalosis

Disopyramide

Uses: Arrhythmia

MoA: Sodium channel inhibitor, prolongs repolarization

Dose: PO 10–25 mg/kg/d q6hr

AE: Urine retention, Dry mouth, Constipation

Note: Avoid in heart block.

Dobutamine

Uses: Hypotension, Shock (sp. cardiogenic shock).

MoA: Dopaminergic and β_1 adrenergic effect (Inotrope with vasodilatation).

Dose: IV infusion 2–20 µg/kg/min (titrate to response).

AE: Tachycardia/arrhythmia, Parasthesia.

Note: *Avoid in aortic stenosis. Do not mix with $NaHCO_3$*

Domperidone

Uses: Vomiting, GERD

MoA: Dopamine antagonist

Dose: PO 0.2–0.4 mg/kg/dose q8hr (max 20 mg/dose)

AE: Drowsiness/agitation, Gynecomastia

Dopamine

Uses: Hypotension, Shock

MoA: Dopaminergic and β_1 adrenergic effect (Inotrope with vasodilatation). α-adrenegic effect with peripheral vasoconstriction in high doses

Dose: IV infusion 2–20 µg/kg/min* (titrate to response).

AE: Tachycardia, Arrhythmia, Thrombophlebitis.

*Do not mix with $NaHCO_3$

Note: Add 15 mg/kg drug in 24 ml NS/DNS. Infusion rate of 0.5 ml/hr equals 5 µg/kg/min

Droperidol

Uses: Psychosis, Anti-emetic

MoA: Dopamine antagonist

Dose: IV 0.03–0.07 mg/kg/dose q6hr.

AE: Extrapyramidal reactions, Hypotension

Drotaverine

Uses: Recurrent Functional abdominal pain, Renal colic

MoA: Phosphodiesterase inhibitor- Smooth muscle relaxant

Doses: PO 20 mg/dose (1–5 yr), 40 mg/dose (>5 yr) q8hr

AE: dry mouth, Vomiting, Fainting-

Edrophonium Hydrochloride

Uses: Diagnosis of Myasthenia gravis (Tensilon test).

MOA: Cholinesterase inhibitor.

Dose: IV 0.1–0.2 mg/kg, improvement for 1–2 min within seconds

AE: Arrhythmia, hypotension, bronchospasm.

Note: Avoided in young children, in whom Neostigmine test may be used

EDTA (Edetate Calcium Disodium)

Uses: Lead poisoning

MoA: Chelating agent

Dose: IV 1000 mg/m^2/d × 5 days

AE: Hypotension, Arrhythmia, Seizure, Rash, Nephrotoxicity

Note: Contraindicated in renal failure and tuberculosis.

Epinephrine: See adrenaline

Enalapril

Use: Hypertension, CCF

MoA: Angiotensin-converting enzyme (ACE) inhibitor.

Dose: As per route of administration:

- PO 0.1–0.5 mg/kg/d q12–24hr (start with lower dose)
- IV 0.01–0.02 mg/kg/d q12–24hr

AE: Hypotension, Hyperkalemia, Hypoglycemia.

Note: Contraindicated in bilateral renal artery stenosis.

Enoxaparin

Uses: Anticoagulant, e.g. Deep vein thrombosis.

MoA: Low molecular weight Heparin -binds antithrombin to form a complex that irreversibly inactivates clotting factor Xa.

Dose: As per indications:

- ***Treatment:*** 1mg/kg/dose q12hr (1.5 mg/kg in infants)
- ***Prophylaxis:*** 0.5 mg/kg/dose q12hr (0.75 mg/kg in infants)

AE: Bleeding, Hypertension, Renal injury

Ergotamine

Uses: Severe migraine - to prevent or abort the attack.

MoA: α-adrenergic blocker, causes vasaoconstriction.

Dose: SL/PO 1 mg at onset of attack

AE: Vasospasm, Leg cramps, Parasthesia

Erythropoietin

Uses: Severe anemia of prematurity, Chronic renal disease, Bone marrow suppression

MoA: Erythropoiesis stimulant

Dose: SC/IV 50–100 U/kg/dose alternate day

AE: Local pain and reactions, Dizziness, Rash, Arthalgia

Esmolol

Use: Severe hypertension

MoA: Selective β_1 adrenergic blocker

Dose: IV 100–500 µg/kg (L) > 25–500 µg/kg/min

AE: Dizziness, Bronchospasm

Note: Contraindicated in CCF and heart blocks

Ethacrynic Acid

Use: Diuretics - Moderate/severe edema or fluid overload.

MoA: Loop diuretic (acts on Loop of Henle)

Dose: PO 1–3 mg/kg/d q8–24hr

AE: Hypovolemia, Hypokalemia, Hyperuricemia

Ethosuximide

Use: Epilepsy (sp. absence seizures)

MoA: Calcium channel blocker

Dose: PO 15–40 mg/kg q12hr (start with lower dose)

AE: Sedation, GIT upsets, Rash, Pancytopenia.

Note: Similar drug: Methsuximide PO 10–30 mg/kg/d q6–8hr.

Famotidine

Uses: Acute/chronic Gastritis, GERD

MoA: H_2 receptor antagonist

Dose: PO/IV 1–1.5 mg/kg/d q12hr

AE: Thrombocytopenia

Fentanyl

Use: Pre-operative sedation, analgesia

MoA: Narcotic (Opioid) analgesic

Dose: As per route of administration:
- IV 1–3 µg/kg/dose q30–60 min, *or*
- IV 1–5 µg/kg/hr as infusion, *or*
- PO: 10–15 µg/kg/dose

AE: Hypotension, Respiratory depression, Vomiting

Fexofenadine

Uses: Allergic conditions (not for use < 6 mo age)

MoA: Antihistamine - H_1 receptor antagonist.

Dose: PO 15 mg (6 mo–2 yr) or 30 mg (> 2yr) /dose q24hr

AE: Sedation, Paradoxical hyperactivity, Dry mouth

Filgastrim (G-CSF)

Uses: Severe neutropenia

MoA: Granulocyte colony stimulating factor.

Dose: IV 10 µg/kg/d q24hr (till ANC < 1000/mm^3)

AE: Hypotension, Vasculitis, Thrombocytopenia, Bone pains.

Fludrocortisone

Uses: Mineralocorticoid insufficiency, e.g. in CAH

MoA: Hormone replacement therapy

Dose: PO 0.05–0.2 mg/d q12–24hr

AE: Hypertension, Edema, CCF, Hypokalemia

Flumazenil

Uses: Diazepam/other Benzodiazepine poisoning.

MoA: Antidote - antagonist on GABA receptors.

Dose: IV 0.01 mg/kg (max 0.2 mg) repeat q1min (Total 1 mg)

AE: Hyper/hypotension, Arrhythmia, Seizures

Fluoxetine

Uses: Obsessive-compulsive behavior (Not for use < 5 yr)

MoA: Inhibits serotonin uptake in CNS

Dose: PO 5–10 mg/d titrate up slowly to max 20 mg/d

AE: Anxiety, Tremors, Insomnia, Suicidal tendencies

Fluticasone

Use: Asthma (maintenance), Allergic Rhinitis

MoA: Long-acting steroid.

Dose: As per indication:
- Asthma: MDI/DPI: 100 - >800 µg/d q12hr
- Allergic Rhinitis: Nasal spray 50–100 µg/d q24hr

AE: Thrush – prevent oral thrush by gargles after inhalation

Folic Acid

Uses: Megaloblastic anemia, prevention of Neural tube defects (NTD)

MoA: Nutrition supplement

Dose: As per indications:
- *Megaloblastic anemia*: PO 1–5 mg q24hr × 3–4 wk*
- *Prevention of NTD*: PO 0.4 mg q24hr (*or* PO 5 mg q24hr in mothers with previous NTD birth) from 1 month before conception to the end of first trimester.

AE: Large Folic acid doses may unmask Vit B_{12} deficiency and worsen neurological problems despite correction of anemia

Note: All severe cases should also receive Vit B_{12} 1 mg/d along with folic acid.

Formoterol

Use: Asthma (Long-term control)

MoA: Selective β_2 agonist (Long-acting)

Dose: MDI/DPI 12–24 µg/d q12–24hr.

AE: Tremors, palpitation/tachycardia, hypokalemia.

Note: Not used as monotherapy, only in combination with inhaled steroids.

Fosphenytoin

Uses: Status Epilepticus

MoA: Sodium channel inhibitor

Dose: IV 15–20mg/kg/d (L) > 4–6 mg/kg/d

AE: Ataxia, Pruritis, Steven-Johnson syndrome

Furosemide

Use: Moderate/severe edema or fluid overload

MoA: Loop diuretic, acts on loop of Henle.

Dose: IV/PO 1–2 mg/kg/d q12–24hr (max 6mg/kg) *or*
IV 0.1–0.4 mg/kg/hr infusion

AE: Hypovolemia, Hypokalemia, Hyperuricemia, Hypercalciuria

Gabapentin

Use: Epilepsy (Add-on drug in partial seizures)

MoA: GABA Analog - potentiates neuroinhibitory GABA action

Dose: PO 15 mg/kg/d q8hr (titrate up to max 50 mg/kg/d).

AE: Ataxia, tremors, Weight gain (Not for use <12 yrs age)

Glycerin

Uses: Laxative

MoA: Lubricant and osmotic Laxative

Dose: PR suppository 1.5–3.0 gm *or* Enema 30–50 ml.

AE: Recurrent soiling of cloths, when used as laxative.

Note: Also used as vehicle for drugs and dressings (with Magnesium sulfate)

Glycerol (50–70%)

Uses: Mild Cerebral edema, Glaucoma

MoA: Osmotic Diuretic, lowers intracranial/intraocular pressure

Dose: PO 1.0–1.5 gm/kg/dose q12–24hr

AE: Hyperglycemia, Hemolysis, Nephrotoxic

Granisetron

Uses: Chemotherapy induced nausea/vomiting

MoA: 5-HT receptor antagonist.

Dose: IV 40 µg/kg or PO 1–2 mg, 30 min before chemotherapy

AE: Arrhythmia, Agitation

Glucagon

Use: Refractory hypoglycemia.

MoA: Stimulates glycogenolysis and neoglucogenesis.

Dose: IV/IM/SC 0.025–0.3 mg/kg/dose, q20 min if required

AE: Hyperglycemia, hypersensitivity reactions

Growth Hormone

Uses: Growth hormone deficiency, Short stature

MoA: Hormonal replacement therapy (Ch 22.2.2)

Dose: SC 25–50 µg/kg OD (100 µg/kg in Puberty*)

AE: Local lipoatrophy, pseudotumor cerebri, hyperglycemia

Note: Continue till bone age > 14 years in girls and 16 years in boys or growth velocity falls to <2 cm/year or desired height is achieved, whichever is earlier.

Haloperidol

Uses: Tranquilizer, Chorea

MoA: Competitive blockade of dopamine receptors.

Dose: As per indication and severity (Avoid < 6 yr age) -

- Tranquilizer: PO 0.05–0.15 mg/kg/d q8hr
- Chorea: PO 0.01–0.03 mg/kg/d q8hr

AE: Extrapyramidal reactions, Neuroleptic malignant syndrome

Heparin (Unfractionated)

Uses: Prevention/treatment of thromboembolism, also used to maintain patency of IV catheters.

MoA: Anticoagulant - potentiates antithrombin-III action.

Dose: As per indications:

- *Thromboembolism:* 50 U/kg IV bolus > 15–30 U/Kg/hr.*
- *Catheter patency:* 0.5–1.0 U/ml.

AE: Bleeding tendency.

Note: Titrate to maintain APTT 1.5–2.5 times of normal.

Hepatitis B Immunoglobulin (HBIG)

Uses: To prevent HBV infection on exposure, specially in newborns of HBV positive mothers.

MoA: Passive immunization

Dose: As follows:

- Perinatal exposure: IM 0.5 ml within 24 hr of birth (with HBV on other thigh).
- Postnatal exposure: 0.06 ml/kg or 40 IU/kg

AE: None.

Human Normal (Non-specific) Immunoglobulins

Uses: High-risk contacts of measles, Varicella or HAV

MoA: Prophylaxis to prevent/reduce severity of disease

Doses: As per indications:

- Measles: IM 0.25 ml/kg within 6 days of exposure
- Hepatitis A: IM 0.1 ml/kg within 14 days
- Varicella: IM 0.6–1.2 ml/kg within 3 days

AE: Coagulopathy, Thrombocytopenia

Note: Contraindicated in IgA deficiency

Human Rabies Immunoglobulin (HRIG)

Use: Grade III animal bite in previously unimmunized children

MoA: To destroy the virus before attachment to neurons.

Dose: Local infiltration 20 U/kg at the site of exposure, as early as possible*.

AE: Allergic reactions (rare).

Note: May be given up to 7 days of bite. If calculated dose is insufficient to infiltrate all wounds, dilute in normal saline to increase the volume. HRIG is not indicated in re-exposed children,who have received ARV earlier.

Human Tetanus Immunoglobulins (TIG)

Uses: Treatment and prophylaxis of tetanus in unimmunized children.

MoA: Neutralization of tetanus toxin

Dose: As per indications:
- *Treatment*: IM 3000–6000 IU (not 30–300 IU/kg or 10000 IU
- *Prophylaxis*: IM 250 IU

AE: Allergic reactions (rare).

Hydralazine

Uses: Hypertension, CCF

MoA: Direct arteriolar vasodilator.

Dose: As per route of administration:
- IV 0.1–0.2 mg/kg/dose q4–6hr (max 20 mg/dose).
- PO 0.75-3.0 mg/kg/d q6-12hr (max 7 mg/kg/d).

AE: Tachycardia/palpitation, Lupus-like reactions

Hydrochlorothizide

Uses: Diuretic, Hypertension, Hypercalciuria treatment

MoA: Inhibits Na^+/Cl^- reabsorption at distal tubules.

Dose: PO 2–3 mg/kg/d q12hr (max 50 mg/d)

AE: Hyperglycemia, Hyperuricemia, Blood dyscrasia

Hydrocortisone

Uses: Allergy/inflammatory conditions, septic shock, Status asthmaticus, Cerebral edema. Congenital adrenal insufficiency (CAH).

MoA: Glucocorticoid - Short-acting.

Dose: As per indications:
- *Septic shock*: 50–150 mg/m^2/d q6hr
- *Status asthmaticus*: IV 4–8 mg/kg/dose q6hr or 50–100 mg/dose q6hr
- *CAH*: IV 1–2 mg/kg, then PO 15–20 mg/m^2/d q6hr (Life-long)

AE: Hypertension, hyperglycemia, fluid retention

Hydroxyurea

Uses: Cancer chemotherapy, Sickle cell anemia, Polycythemia vera, etc.

MoA: Blocks DNA synthesis, stimulates HbF production.

Dose: As per indications:
- *Sickle cell disease:* PO 10–15 mg/kg q24hr (>2 yr age)
- *Cancers:* as above *or* 1500–3000 mg/m^2 q4–6 wks.

AE: Gastric upset, mucositis, headache, rash, myelosuppression, hepatitis, hyperuricemia

Hydroxyzine

Uses: Allergic conditions

MoA: Antihistamine - H_1 receptor antagonist

Dose: PO/IM 0.5–1 mg kg/dose q8hr

AE: Sedation, Paradoxical hyperactivity, Dry mouth

Ibuprofen

Uses: NSAID, PDA closure in Preterms

MoA: Prostaglandin synthesis inhibitor

Dose: As per indications:
- General: PO 10 mg/kg/dose q8hr
- Rheumatoid arthritis: 30–70 mg/kg/d q4–6hr
- PDA: IV/PO 10 mg/kg > 5 mg/kg after 24 and 48 hrs

A/E: Gastritis, Nephrotoxicity (avoid in renal disease)

Impiramine (Depsonil)

Use: Antidepressant, Nocturnal enuresis.

MoA: Increases synaptic neurotransmitter concentration.

Dose: As per indications:
- *Depression*: 1.5–5.0 mg/kg/d (start with lower dose).
- Enuresis: 10–25 mg at bed time (max 50 mg/dose)

AE: Postural hypotension, Sedation, Constipation

Indomethacin

Uses: NSAID, PDA closure in Preterms

MoA: Prostaglandin synthesis inhibitor

Dose: As per indications:
- General: PO 2–3 mg/kg/d q12–24hr
- PDA: IV 0.2 mg/kg/dose at 0, 12, 24 hr (3 doses)

A/E: Gastritis, Hypoglycaemia, Nephrotoxicity

Insulin

Use: Diabetes (DKA, IDDM), hyperkalemia

MoA: Hormonal replacement

Dose: As per indications:
- *Diabetes: See* Ch 22.7
- *Hyperkalemia*: IV 0.1–0.3 U/kg/hr in 1 ml/kg DW 50% over 1 hr

AE: Hyperglycemia, Insulin resistance, Lipodystrophy

Intravenous Immunoglobulins (IVIG)*

Uses: ITP, GBS, Kawasaki disease, Primary Immunodeficiency (PID)

MoA: Bind with causative antibodies, passive prophylaxis

Dose: PID: IV 300–400 mg/kg q4wk

Others: IV 400 mg/kg/d × 5 days *or* 1 gm/kg/d × 2 days *or* 2 mg/kg/d once only

AE: Headache, flushing, Wheezing

**Also see Ch..9.9*

Iron

Use: Iron deficiency anemia

MoA: Nutritional supplement

Dose: (as elemental iron):

- Treatment: PO 3–6 mg/kg/d q8–12hr × 2–3 mo
- Prophylaxis: PO 1–2 mg/kg q24hr

See Ch 19.4.1 for details of parenteral iron therapy and NIPI guidelines

AE: Constipation, GIT upset

Note: Black discoloration of oral mucosa and stools is common after oral iron therapy.

Isoproterenol (Isoprenaline)

Uses: Hypotension, Shock

MoA: Combined β_1 and β_2 agonist (Inotrope with peripheral vasodilation)

Dose: IV 0.5–5.0 µg/kg/min

AE: Palpitation, tremors, Paradoxical bronchospasm

Ipratroprium Bromide

Uses: Asthma – Acute attack/status asthmatics

MoA: Anticholinergic agent.

Dose: As per route of administration:

- *Nebulization:* 250–500 µg/dose, may repeat thrice every 20 min
- *MDI:* 20–40 µg/dose q6–8hr, may repeat thrice every 20 min

AE: Dry mouth, blurred vision, flushing, urinary retention

Isotretinoin

Use: Severe acne - prevention*.

MoA: A Retinoic acid derivative.

Dose: PO 0.5–1.0 mg/kg/d × 3–4 months.

AE: Nil.

Note: Use with topical Tretinoin cream 0.1–1.0% once a day.

Kayoxalate (Sodium Polysterene Sulfonate)

Use: Control of chronic hyperkalemia, e.g. in CKD

MoA: Ion-exchange resin - removes potassium for sodium.

Dose: PO/PR 4–8 gm/kg/d q4–8hr (Max 15 gm/dose).

AE: Hypokalemia, abdominal pain.

Ketamine

Uses: Anesthetic agent for short procedures

MoA: Direct action on cortex and limbic system

Dose: IV 1.0–1.5 mg/kg/dose @ <0.5 mg/kg/min

or IM/PO/PR: 3–10 mg/kg/dose

AE: Hallucination, Vomiting, Respiratory depression

Ketorolac

Use: NSAID, sp. for musculoskeletal pain

MoA: Prostaglandin synthesis inhibitor

Dose: IV/IM/PO 0.4–1.0 mg/kg/dose q6hr

AE: Gastritis, Platelet dysfunction, Nephrotoxicity

Ketotifen

Use: Long-term control – asthma and allergic disorders

MoA: Mast-cell stabilizer

Dose: PO 1 mg/dose q12hr

AE: Dry mouth, skin rash, weight gain, dizziness

Labetelol

Use: Hypertension, including hypertensive crisis

MoA: β and α_1 adrenergic blocker

Dose: As per route of administration:

- IV 0.2–1.0 mg/kg/hr (max 3 mg/kg/hr)
- PO 4 mg/kg/d q12hr (max 40 mg/kg/d)

AE: Hypoglycemia, Bronchospasm

Lactulose

Use: Constipation, hepatic encephalopathy.

MoA: Osmotic laxative, acidifies stool to enhance ammonia excretion.

Dose: As per indications:

- *Laxative*: 1–3 ml/kg/d q8–12hr (max 60 ml/d)
- *Hepatic encephalopathy*: 30–50 ml/d q6–8hr*.

*adjust dose to produce 2–3 soft stools/day

AE: Flatulence, Diarrhea

Lamotrigine

Uses: Refractory seizures, e.g. Lennox-Gastaut syndrome.

MoA: Sodium-channel inhibitor

Dose: PO 0.6 mg/kg/d q12hr (max 5–15 mgkg/d)*

AE: Rash (3–5%)*, Ataxia, Headache, Diplopia

Note: Increase gradually by doubling the dose alternate week to reduce the risk of rash, which may be fatal. Discontinue drug immediately, if rash develops. Use lower ($1/4^{th}$) doses in patient on valproate.

Lansoprazole

Uses: Gastritis, Peptic ulcer, GERD

MoA: Proton-pump inhibitor (PPI)

Dose: PO 1 mg/kg/d q24hr *or*

PO 15 mg/d (1–10 yr), 20 mg (>10 yr)

AE: Drowsiness, GIT upset, Headache

Leukovorin

Uses: To prevent folate deficiency on therapy with folate antagonists, e.g. methotrexate.

MoA: Reduced form of folic acid

Dose: IV/PO 10–100 mg/m^2 q6hr.

AE: Rash, Erythema

Levetiracitam

Uses: Epilepsy (Broad spectrum)

MoA: bind synaptic vesicle protein (SV2A) to block release of neurotransmitter

Dose: PO 7–10 mg/kg/dose q12hr, double the dose alternate week, if required. (max 30 mg/kg q12hr)

AE: Behavioral and neuropsychiatric problems

Levocetrizine

Uses: Allergic conditions (Not < 6 mo age)

MoA: Long-acting antihistamine - H_1 receptor antagonist

Dose: PO 0.1 mg/kg q24hr or

PO 2.5 mg q24hr (<6 yr), 5.0 mg q24hr (>6 yr)

AE: Mild sedation (less than other antihistamines)

Levosalbutamol

Uses: Asthma – Acute attack/status asthmatics

MoA: Selective β_2 agonist (Short-acting)

Dose: As per route of administration:

- *Nebulization*: 0.075 mg/kg, may repeat thrice every 20 min
- *PO*: 0.05–0.1 mg/kg/dose q8hr

AE: Tacardia,Tremors, Anxiety, Hypokalemia

Levothyroxine (Eltroxin)

Uses: Hypothyroidism.

MoA: Hormonal replacement therapy.

Dose: PO 4–8 µg/kg q24hr (start with lower dose).

AE: Tachyarrhythmia, Diarrhea, Insomnia, Cramps

Lidocaine

Uses: Arrhythmia, Local anesthetic

MoA: Sodium channel inhibitor.

Dose: IV 1 mg/kg (L), then 20–50 µg/kg/min

AE: Hypotension, Seizures

Note: Contraindicated in heart block

Lithium

Uses: Acute mania, Depression, Bipolar disorders

MoA: alters Cation exchange across cell membrane

Dose: PO 15 mg/kg/d titrate up (max 60 mg/kg/d)

AE: Nephrotoxicity, Rash, Goiter, Tremors

Note: To be used by Psychiatrist only, No breastfeeding by mothers on lithium.

Loratidine

Uses: Allergic conditions (Not < 6 mo age)

MoA: Long-acting Antihistamine - H_1 receptor antagonist.

Dose: PO 0.2 mg/kg q24hr or

PO 5 mg q24hr (10 mg q24hr >12 yr).

AE: Mild sedation (less than other antihistamines)

Lorazepam

Uses: Status epilepticus, Anxiety, Sedation

MoA: Benzodiazepine - potentiates neuroinhibitory GABA action

Dose: As per indications:

- S. epilepticus: IV/PR 0.1–0.2 mg/kg/dose (max 4 mg), repeat every 15 min if required
- Anxiety/sedation: IV/PO 0.05–0.1 mg/kg/dose q4–6hr

AE: Sedation, Paradoxical excitation, Myoclonus

Magnesium Hydroxide (Milk of Magnesia)

Use: Constipation

MoA: Osmotic laxative

Dose: PO 0.5–1.0 ml/kg/dose at bed time

AE: Abdominal cramps, Diarrhea

Magnesium Sulfate (50%)

Use: Hypomagnesemic tetany, Asthma

MoA: Electrolyte supplement, smooth muscle relaxation

Dose: As per indications:

- *Tetany/Asthma* : IV/IM 25–50 mg/kg diluted 5–10 times in NS over 30 min. may be repeated q6hr (max 200 mgkg/d)
- *Malnutrition* (supplement): PO 0.3 ml/kg (max 2 ml) on day 1, then 2–3 mEq*/kg q24hr

AE: Hypermagnesemia, Hypotension, Muscle weakness

Note: Each ml contains 4 mEq magnesium

Mannitol

Uses: Cerebral edema, Raised intracranial pressure (ICP), Raised intraocular pressure

MoA: Osmotic diuretic

Dose: IV 1.0 gm/kg q6–8hr (*infuse rapidly*)

AE: Circulatory overload, Electrolyte imbalance

Mefenemic Acid

Uses: NSAID, sp. for fever, chronic arthritis

MoA: Prostaglandin synthesis inhibitor

Dose: As per indications:

- General: 5–7 mg/kg/dose q8hr
- Arthritis: 25 mg/kg/d q6hr

AE: Rash, Diarrhea

Melatonin

Uses: Insomnia

MoA: Regulates diurnal sleep-wake cycle

Dose: PO 6 mg at bedtime (3 mg in 1–12 yr)

AE: Day-time drowsiness, Dizziness

Mesna

Use: To prevent hemorrhagic cystitis on cyclophosphamide therapy.

MoA: Binds urotoxic metabolites of cyclophosphamide.

Dose: IV/PO 20–40% w/w cyclophosphamide q4hr (from 3 hours before to 12 hour after the dose).

AE: Hypotension, Vomiting, Headache, Limb pains.

Metaclopramide

Uses: Vomiting, GERD

MoA: Dopamine antagonist.

Dose: IV/PO 0.1–0.2 mg/kg/dose q8hr (max 10 mg/dose)

AE: Extrapyramidal reactions. Drowsiness

Methimazole

Uses: Hyperthyroidism.

MoA: Peroxidase inhibitor, blocks thyroxine synthesis.

Dose: PO 0.5–0.7 mg/kg/d q8–24hr > 0.2 mg/kg/d

AE: Blood dyscrasia, Lupus-like syndrome, Hepatitis

Methocarbamol

Uses: Skeletal muscle relaxant, muscle spasm in tetanus.

MoA: CNS depressive effect.

Dose: IV/PO 15–25 mg/kg q6hr (Not to use > 3 days)

AE: Syncope, Hypotension, Drowsiness.

Methotrexate

Uses: Neoplasms, Rheumatoid arthritis.

MoA: Antimetabolite - (Folate antagonist), inhibits DNA and purine synthesis.

Dose: As per indications:

- *JRA:* PO 5–15 mg/m^2/dose weekly
- *Neoplasms:* as per specific protocols

AE: Myelosuppression, Hepatotoxicity, Nephrotoxicity.

Note: Avoid in severe hepatic or renal dysfunction. Give with folic acid.

Methyldopa

Use: Antihypertensive agent

MoA: α_2 adrenergic antagonist

Dose: As per route of administration:

- 20–40 mg/kg/d q6–8hr (max 10 mg/kg/dose)
- PO 10–40 mg/kg/d q6–8hr (max 3 gm/d)

AE: Edema, Hepatotoxicity, Hemolytic anemia

Methylene Blue

Use: Methemoglobinemia (Naphthalene poisoning)

MoA: Antidote - reduces Iron in Hemoglobin (Ferric >ferrous state)

Dose: IV 1–2 mg/kg over 15–30 min, q1hr, if required

AE: Dizziness, Headache, Hemolysis in G6PD deficiency

Methylphenidate

Uses: Attention deficit-hyperactivity disorder

MoA: CNS stimulant

Dose: (Not for use < 5 years)

- PO 0.3–0.6 mg/kg/dose q24hr after meals* *or*
- PO 5 mg/dose q24hr > titrate slowly to max 60 mg/day

AE: Insomnia, Hypertension, Growth failure.

Note: Should not be given after 4 PM to avoid insomnia

Methylprednisolone

Uses: Allergy/inflammatory/autoimmune/malignant conditions, Acute spinal cord injury.

MoA: Intermediate-acting corticosteroid.

Dose: As per indications:

- *General:* IV/PO 0.5–2.0 mg/kg/d q6–12hr
- *High-dose pulse therapy*: 15–30 mg/kg q24hr × 3–5 days
- *Spinal cord injury:* IV 30 mg/kg (L) > 5.4 mg/kg/hr

AE: Hypertension, Hyperglycemia, Fluid retention

Metolazone

Uses: Diuretic - Moderate/severe edema/Fluid overload

MoA: Inhibits sodium reabsorption at distal tubules

Dose: PO 0.2–0.4 mg/kg/d q12–24hr

AE: Dehydration, Hypocalcemia, Hyperglycemia

Metoprolol

Use: Hypertension

MoA: Selective β_1 adrenergic blocker

Dose: As per route of administration:

- PO 1–5 mg/kg/d q12hr
- IV 0.1 mg/kg/dose q12hr

AE: Dizziness, Heart block

Note: Contraindicated in CCF

Midazolam

Uses: Status epilepticus, Pre-procedure sedation

MoA: Benzodiazepine-potentiates neuroinhibitory GABA action.

Dose: As per indications:
- Seizures: IV 0.2 mg/kg, then 0.1–0.2 mg/kg/hr
- Nasal spray: 0.2 mg/kg
- Sedation: IV 0.01–0.2 mg, then > 0.5–3 µg/kg/min

AE: Respiratory depression, Myoclonic movements

Milrinone

Uses: Low-output CCF/Shock, as adjuvant.

MoA: Phosphodiasterase inhibitor (Inotrope and vasodilator)

Dose: IV 50–75 µg/kg (L) > 0.5–1.0 µg/kg/min

AE: Hypotension, Arrhythmia, Thrombocytopenia

Note: Contraindicated in Severer Aortic/pulmonary stenosis

Minoxidil

Use: Refractory Hypertension

MoA: Direct vasodilator

Dose: PO 0.2 mg/kg/d q24hr (max 5 mg/d)

AE: Dizziness, CCF, Hyperetrichosis

Note: Contraindicated in CCF, heart blocks.

Montelukast

Uses: Long-term control – asthma and allergic disorders

MoA: Leukotriene-receptor antagonist

Dose: PO 4 mg q24hr in evening (5 mg above 5 yr age)

AE: Dizziness, Rash, Arthalgia

Morphine

Uses: Severe pain, Left ventricular failure.

MoA: Narcotic (Opioid) analgesic

Dose: As per mode of administration:
- IV/SC 0.1–0.2 mg/kg/dose q4hr (max 15mg) or
- IV 0.01–0.02 mg/kg/hr

AE: Respiratory depression, sedation, dependence

Note: Antidote: *Naloxone (IV 0.01mg/kg) see Ch 27.6.2.*

Mycophenolate Mofetil

Use: Frequent relapse/Steroid-dependent Nephrotic syndrome, Prevention of Transplant rejection.

MoA: Immunosuppressant, inhibits an enzyme required for growth of T and B cells.

Dose: PO 600–1200 mg/m^2/d q8–12hr

AE: Bone marrow suppression

Naloxone

Uses: Morphine poisoning.

MoA: Antidote-Opiate receptor antagonist.

Dose: IV 0.1 mg/kg/dose repeat q2–3 min, as needed

AE: Withdrawal reactions.

Naproxen

Uses: NSAID, Rheumatic disorders

MoA: Prostaglandin synthesis inhibitor

Dose: As per indications:
- General: PO 5–7 mg/kg/dose q8–12hr
- Rheumatic disorders: PO 10–20 mg/kg/d q12hr

AE: Gastritis, Rash, Nephrotoxicity.

Neostigmine

Uses: Diagnosis (challenge test) and treatment of myasthenia gravis in children

MoA: Cholinesterase inhibitor

Dose: As per indication:
- *Challenge test:* IM 0.02–0.04 mg/kg (max effect in 20–40 min)
- *Treatment:* IV/SC 0.01–0.04 mg/kg q2–4hr *or* PO 1–3 mg/kg/d q4–6hr
- *Newborns:* IM/SC 0.05–0.1 mg > PO 1 mg before feeds

AE: Flushing, palpitation/tachycardia.

Niacin (Vitamin B_3)

Uses: Pellagra, Hyperlipidemia

MoA: Nutritional supplement

Dose: PO 50–300 mg q24hr

AE: Flushing at injection site, Cholestatic jaundice.

Nicardipine

Use: Hypertensive crisis

MoA: calcium channel blocker

Dose: IV1–3 µg/kg/min

AE: Palpitation, Chest pain, Flushing

Nifedipine

Uses: Hypertension, Hypertrophic cardiomyopathy.

MoA: Calcium-channel blocker.

Dose: PO/SL 0.25-1 mg/kg/d q6–8hr

AE: Facial flushing, Hypotension.

Nitrazepam

Uses: Epilepsy, sp Myoclonic seizures

MoA: Sodium-channel inhibitor.

Dose: PO 0.2–1.0 mg/kg/d q8hr (start with lower dose).

AE: Drowsiness, Behavioral problems, Hallucinations

Noradrenaline (Norepinephrine)

Uses: Hypotension, shock.

MoA: α_1 Adrenergic agonist.

Dose: IV 0.05–0.1 mg/kg/min, titrate upto max 2 mg/kg/min.

AE: Hypertension, Arrhythmia, Headache

Octrotide

Uses: Acromegaly, esophageal variceal bleeding, secretory diarrhea in vasoactive gut tumors.

MoA: Somatostatin analogue, binds somatostatin receptors to block Growth hormone activity and reduce splanchnic blood flow.

Dose: *As per indications:*

- *Acromegaly:* IM Octreotide 1–40 µg/kg/d
- *Varices:* IV 1–10 µg/kg/hr (or q12hr), till bleeding is controlled

AE: Local Flushing, Hypo/hyperglycemia, Arrhythmia, pancreatitis

Omeprazole

Uses: Gastritis, Peptic ulcer, GERD

MoA: Proton-pump inhibitor

Dose: PO 0.6–0.7 mg/kg/d q24hr *or*
PO 10 mg/d (10–20 kg), 20 mg/d (>20 kg).

AE: Drowsiness, Headache, Hepatotoxic on prolonged use

Ondensetron

Uses: Anti-emetic : Vomiting, GERD

MoA: 5-HT receptor antagonist.

Dose: As per route of administration:

- IV: 0.1–0.2 mg/kg/dose q8hr (max 8 mg/dose)
- PO: 4–8 mg q8hr.

AE: Headache, chest pain.

Orciprenaline

Uses: Asthma – Acute attack/status

MoA: selective $\beta_2$agonist.

Dose: As per route of administration:

- PO: 0.5–2.0 mg/kg/dose q6–8hr.
- Nebulization: 0.01–0.02 ml/kg/dose (5% sol).

AE: Tachycardia,Tremors, Anxiety, Hypokalemia

Oxybutynin

Uses: Urinary anti-spasmodic.

MoA: Anticholinergic - Smooth muscle relaxant.

Dose: PO 0.2 mg/kg/dose q6–8hr.

AE: Sedation, Dry mouth, Blurred vision.

Pancuronium

Uses: Anesthesia, Muscle relaxant

MoA: Non-depolarising neuromuscular antagonist

Dose: IV 0.04–0.1 mg/kg/dose, repeat q20–30 min

AE: Hypertension, Prolonged muscle weakness

Pantoprazole

Uses: Gastritis, Peptic ulcer, GERD

MoA: Proton-pump inhibitor (PPI)

Dose: PO 0.6–1.2 mg/kg/d (max 15 mg/d in infants) *or*
PO 20 mg/d (2–5 yr), 40 mg/d (> 5yr)

AE: Nephrotoxic on prolonged use

Paracetamol (Acetaminophen)

Uses: NSAID sp. as antipyretic, analgesic, PDA closure.

MoA: Prostaglandin synthesis inhibitor

Dose: As per indications:

- General: PO 10–15 mg/kg/dose q4–6hr or
  IV 7.5–15 mg/kg/dose q6hr
- PDA closure: IV 15 mg/kg/dose q6hr × 3 days

AE: None, Hepatotoxic on overdose

Note: Antidote: N-acetylcysteine (See Ch 27.6.2)

Pemoline

Uses: Attention deficit-hyperactivity disorder

MoA: CNS stimulant

Dose: PO 1–3 mg/kg/d q24hr in morning

AE: Seizures, Movement disorders, Hypertension

Penicillamine

Uses: Wilson disease, Lead poisoning

MoA: Copper and Lead chelating agent

Dose: As per indications:

- Wilson disease: PO 20 mg/kg/d q6–12hr
- Lead poisoning: PO 25–30 mg/kg/d q8–12hr

AE: Blood dyscrasia, Rash, Lupus-like syndrome, Renal dysfunction

Pentazocine

Uses: Severe pain sp. in trauma, surgery

MoA: Narcotic (Opioid) analgesic

Dose: IV/IM 0.5–1.0 mg/kg/dose (Max 30 mg) q3–4hr

AE: CNS depression, respiratory depression.

C/I: Head injury, Raised ICP

Pentobarbital

Uses: Sedation, Refractory status epilepticus

MoA: Barbiturate - short acting.

Dose: IM/PO 10 mg/kg (L) >1–5 mg/kg/hr

AE: Hypotension, respiratory depression

Pentoxyfylline (Trental)

Uses: Peripheral vascular disease, Raynaud syndrome

MoA: Anti-platelet, anti-inflammatory, maintains vascular patency

Dose: PO 20 mg/kg/d q8hr.

AE: Hypotension, Tachycardia

Phenarmine Maleate

Use: Allergic conditions (Not for use < 1 yr)

MoA: Antihistamine - H_1 receptor antagonist.

Dose: PO/IV 0.2 mg/kg/dose q8hr

AE: Sedation, Paradoxical hyperactivity, Dry mouth

Phenazopyridine

Use: Dysuria in UTI/urological procedures.

MoA: Urinary anesthetic.

Dose: PO 12 mg/kg/d q8hr

AE: Rash, Methemoglobinemia.

Phenobarbitone

Use: Status Epilepticus, Sedation, Neonatal hyperbilirubinemia, e.g. Crigler Najjar syndrome

MoA: Chloride-channel facilitator, Microsomal enzyme inducer

Dose: As per indications:

- Seizures: IV 15–20 mg/kg (L) > 5 mg/kg q15 min (twice) > IV/PO 4–6 mg/kg/d q12–24hr
- Sedation: IV/PO 2 mg/kg/dose q12–24hr
- Neonatal hyperbilirubinemia: PO 3–8 mg/kg/d q12–24hr

AE: Drowsiness, Respiratory depression, Behavioral problems

Phenoxybenzamine

Uses: Pheochromocytoma induced hypertension.

MoA: α-adrenergic antagonist

Dose: IV 0.1–0.6 mg/kg q8–12hr (titrate to effect).

AE: Postural hypotension, Syncope.

Phentolamine

Uses: Pheochromocytoma induced hypertension.

MoA: α-adrenergic antagonist.

Dose: IV 0.05–0.1 mg/kg q1–2hr (max 5 mg/dose).

AE: Postural hypotension, palpitation

Phenylephrine

Uses: Shock/hypotension.

MoA: α_1-adrenergic agonist - vasoconstrictor.

Dose: IV 5–20 mg/kg/dose q10–15 min.

AE: Hypertension, angina.

Note: Also used as nasal decongestant in nasal drops/oral cold-cough preparations.

Phenytoin

Uses: Status Epilpticus, Epilepsy, Arrhythmia

MoA: Sodium channel inhibitor.

Dose: As per indications:

- Seizures: IV 15–20 mg/kg (L*) > IV/PO 5–8 mg/kg/d q12hr.
- Arrhythmia: IV 1.25 mg/kg q5–10 min till control (max 15 mg/kg) then, IV/PO 3–6 mg/kg/d q12hr.

AE: Ataxia, Steven-Johnson syndrome. Gingival hypertrophy, Rickets.

**Infuse slowly, not to exceed 1–3 mg/kg/min.*

Note: Contraindicated in Porphyria, heart blocks.

Physostigmine

Uses: Belladonna poisoning*, Myasthenia Gravis

MoA: Antidote - Competitive acetylcholine antagonist

Dose: IV 0.01–0.03 mg/kg (slowly not to exceed 0.5 mg/min) q 5–10 min if required (max dose 2 mg)

AE: Palpitation, Bronchospasm, Fasciculations

**Use only in life-threatening cases with caution.*

Piroxicam

Uses: NSAID, sp. in Rheumatic disorders

MoA: Prostaglandin synthesis inhibitor

Dose: PO 0.2–0.3 mg/kg q24hr

AE: Gastritis, hepatotoxicity (avoid in young children)

Polyethylene Glycol (PEG 3350)

Use: Constipation.(Not for use <8 yr)

MoA: Osmotic laxative

Dose: PO 8.5 gm sachet in a glass of water, multiple sachets or repeat doses may be required

AE: Flatulence, Diarrhea

Potassium Chloride (IV: 10%)

Uses: Treatment of Hypokalemia

MoA: Electrolyte supplement (1 ml = 2 mEq)

Dose: IV: 1–3 mEq/kg/d q8hr (slowly)

AE: Local reaction, Arrhythmia if given rapidly.

Potassium Chloride (Oral: 20 mEq/15 ml)

Use: Prevention and treatment of disease/drug-induced Hypokalemia

MoA: Electrolyte supplement

Dose: PO 2–5 mEq/kg/d q12hr

AE: Vomiting, Hyperkalemia

Pralidoxime (PAM)

Uses: Organophosphorus poisoning.

MoA: Antidote-Acetylcholinesterase re-activator.

Dose: IV 25–50 mg/kg/dose followed by
5 mg/kg/hr *or* 5–10 mg/kg q1–2 hr

AE: Cholinergic effects, e.g. Hypertension, Muscle rigidity.

Prazocin

Uses: Hypertension, Scorpion sting (Autonomic storm)

MoA: α-adrenergic blocker.

Dose: As per indication:
- Hypertension: PO 0.1–0.4 mg/kg/d q6–8hr
- Scopion sting: PO 30 µg/kg/dose at 0, 3, 6 hr

AE: Hypotension, Syncope, Palpitation, Fluid retention

Prednisolone

Uses: Allergy/inflammatory/autoimmune/malignant conditions, sp. Nephrotic syndrome, Rheumatic fever, Asthma, Rheumatoid disorders, CAH.

MoA: Intermediate-acting corticosteroid

Dose**: PO 1–2 mg/kg/d q8–12hr

AE: Cushingoid facies, hypertension, hyperglycemia, immunosuppression, growth failure, Gastritis/peptic ulcer, osteoporosis, cataracts, etc.

Procainamide

Uses: Arrhythmia

MoA: Sodium channel inhibitor, prolongs repolarization.

Dose: As per route of administration:
- IV: 3–6 mg/kg (L) > 20–80 µg/kg/min
- PO: 15–50 mg/kg/d q4–6hr

AE: Heart-block, Blood dyscrasia, Lupus-like syndrome.

Prochlorperazine

Uses: Antiemetic, Antipsychotic (Not for use < 2yr)

MoA: Dopamine antagonist

Dose: PO 0.1–0.2 mg/kg/dose q8–12hr (Not >20 mg/d)

AE: Extrapramidal reactions,

Promethazine (Phenargan)

Uses: Antiallergic, Antiemetic, Sedative (pre-procedure).

MoA: Phenothiazine with antihistaminic effect.

Dose: PO/IV 1 mg/kg/dose q6–8hr (Not for use < 2 yr)

AE: Extrapyramidal reaction, Hypotension, Sedation

Propofol

Uses: Pre-procedure sedation, Mechanical ventilation

MoA: Non-barbiturate sedative.

Dose: IV 1.5–3.0 mg/kg (L) > 0.1–0.3 mg/kg/min

AE: Hypotension, Bradycardia

Propranolol

Uses: Hypertension, Arrhythmia, Cyanotic spells, Hemangioma, Thyrotoxicosis, Migraine prophylaxis

MoA: Non-selective β-adrenergic blocker.

Dose: As per indications:
- Hypertension: PO 0.5–1.0 mg/kg/d q8hr
- Arrhythmia: IV 0.01–0.1 mg/kg/dose q6–8hr
- Others: PO 2–4 mg/kg/d q6–8hr, start with lower dose

AE: Bronchospasm, Hypotension, Hypoglycemia

Note: Avoid in asthma/CCF.

Protamine Sulfate

Uses: Antidote to heparin-induced bleeding.

MoA: heparin antagonist (1 ml protamine neutralizes 100 U of heparin).

Dose: PO 5–7 mg/kg/d q8hr, titrate to effect.

AE: Hypotension. Excess dose may itself cause anticoagulation

Pseudoephedrine

Uses: Nasal decongestant for topical/oral use.

MoA: Indirect sympathomimetic agent

Dose: PO 4 mg/kg/d q6–12hr

AE: Palpitation, tremors.

Note: Avoid in hypertensive and cardiac patients.

Pyridostigmine

Uses: Myasthenia gravis.

MoA: cholinesterase inhibitor.

Dose: As per route of administration:
- PO 7 mg/kg/d, q4–6hr.
- IV/IM 0.05–0.15 mg/kg/dose q4–6hr (max 10 mg/dose).

AE: Bradyarrhythmia, seizures, cholinergic side-effects

Pyridoxine (Vitamin B_6)

Uses: Pyridoxine Deficiency/dependency, Prevention of INH-induced neuritis

MoA: Nutritional supplement

Dose:
- *Deficiency*: PO/IV 50–100 mg q24hr till recovery

- *Dependency*: PO 10–100 mg q24hr or IM 2–5 mg q24hr for life
- *Prevention of INH neuritis*: PO 1 mg/kg q24hr

AE: None, Large IV doses may precipitate seizures

Quinidine Sulfate

Uses: Arrhythmia, very rarely in malaria.

MoA: Sodium channel inhibitor, prolongs repolarization.

Dose: (Arrhythmia) PO 20–60 mg/kg/d q4–6hr

AE: Hypotension, Heart block, Cinchonism.

Note: A test dose of PO 2 mg/kg is advised before first dose.

Rabies Monoclonal Antibodies (Rabishield®/Twinrab®)

Use: Grade III animal bite.

MoA: Block entry of virus into neighboring cells

Dose: Local infiltration* - Rabishield® 3.3 IU/kg, Twinrab® 40 IU/Kg.

AE: None, Hypersensitivity

Note: While most effective when given immediately, may be given up to 7 days of bite. If calculated dose is insufficient to infiltrate all wounds, dilute in normal saline to increase the volume.

Racecadotril

Uses: Secretory diarrhea, e.g. Viral, cholera, Entero-toxigenic E.coli

MoA: Encephalinase inhibitor - increases encephalin concentrations in gut to reduce motility and fluid loss.

Dose: PO 1.5 mg/kg/dose q8hr

AE: None significant

Ranitidine

Uses: Gastritis, GERD

MoA: H_2 receptor antagonist

Dose: PO/IV 2–5 mg/kg/d q8–12hr

AE: Headache, Drowsiness.

Risperidone

Use: Autism, to control aggressive behavior

MoA: Inhibits Serotonin and norepinephrine re-uptake

Dose: PO 0.5 mg/d q24hr, titrate up to max 3.5 mg/d

AE: Drowsiness, Inattention, Blurred vision

Rituximab

Uses: Cancers, Transplant rejection, Autoimmune disorders, e.g. ITP, JRA, etc.

MoA: Monoclonal antibody against CD_{20} cells.

Dose: Varies with indication. See specific diseases.

AE: Severe infusion reactions

Rizatriptan

Uses: Refractory migraine (Not for use < 5 yr)

MoA: 5-HT antagonist

Dose: PO 5 mg/dose (10 mg/dose > 40 kg)

AE: Drowsiness, Dizziness

Salbutamol (Albuterol)

Uses: *Asthma* – Acute attack/status

MoA: Selective β_2 agonist (Short-acting)

Dose: As per route of administration:

- *Nebulization*: 0.15 mg/kg/dose may repeat thrice every 20 min
- *MDI/DPI*: 100–400 µg/dose, may repeat thrice every 20 min
- *PO*: 0.1–0.2 mg/kg/dose q8hr

AE: Tacardia,Tremors, Anxiety, Hypokalemia,

Salmeterol

Uses: Asthma (Long-term control)

MoA: Selective β_2 agonist (Long-acting)

Dose: MDI/DPI 50–100 µg/dose q12–24hr

AE: Same as with salbutamol. (not ffor use < 4 yr)

Note: Not used as monotherapy, only in combination with inhaled steroids.

Sargramostim (Gm-CSF)

Uses: Myelodepression after chemotherapy, Post-transplant

MoA: Granulocyte-macrophage colony stimulating factor

Dose: IV/SC 250 µg/m^2 q24hr (until ANC >1500 cells/mm^3)

AE: Flue-like illness, bone pains, edema, (Avoid < 2 yr)

Sildenafil

Use: Pulmonary hypertension, PPHN

MoA: Vasodilator

Dose: PO 0.3–3.0 mg/kg/d q8hr

IV 0.4 mg/kg over 3 hr, >1.6 mg/kg/d infusion

AE: Dizziness

Simethicone

Uses: Symptomatic relief in Intestinal colic.

MoA: Anti-flatulent

Dose: PO 20–40 mg/kg/dose q6hr

AE: None significant

Sodium Bicarbonate 7.5% (1ml=0.9 mEq)

Uses: Metabolic acidosis, urinary alkalinization in poisonings

MoA: Bicarbonate replacement

Dose: IV 1–3 mEq/Kg/dose, or

- Calculate as follows (*also see Ch 7.6.3*)
- Required $NaHCO_3$ (in mEq)* = (Desired HCO_3 – Actual HCO_3) × Wt × 0.6.

AE: Hypernatremia, metabolic alkalosis, thrombophlebitis.

**Do not do full correction. Correct slowly over 3–4 hr as rapid correction may precipitate tetany due to intracellular movement of calcium. Also treat primary cause, e.g. dehydration or shock.*

**In poisoning, adjust doses to maintain urine pH 7.5–8.0*

Sodium Chloride 3%

Uses: Severe symptomatic hyponatremia

MoA: Electrolyte replacement

Dose: (*also see Ch 7.2*)

- *Acute:* 2 mg/kg/dose in 10 min or 3–5 ml/kg in 1 hr (max 100 ml),
- *Chronic:* calculate as follows*
  Sodium deficit (mEq) = (125 – S. Sodium) × weight × 0.6

AE: Hypernatremia, Seizures on rapid correction.

**Do not correct >10 mEq/L in 24 hours. As thumb rule, 12 ml/kg of 3% NaCl raises S. Na+ levels by ~10 mEq/L.*

Sodium Nitroprusside

Uses: Hypertensive crisis, Resistant CCF

MoA: Direct vasodilator

Dose: IV 0.3–0.5 µg/kg/min in DW5% as 50 µg/ml, titrate up (max 8–10 µg/kg/min)

AE: Cyanide toxicity*, Methemoglobinemia, Hypotension

**Not to use beyond 72 hours*

Spironolactone

Uses: Diuretic - Mild/moderate edema, Ascites, Hypertension

MoA: Aldosterone antagonist (Potassium-sparing)

Dose: PO 1.5–3 mg/kg/d q12–24hr (max 100 mg/d).

AE: Hyperkalemia, CNS dysfunction, Gynecomastia.

Note: Avoid in renal failure.

Streptotokinase

Uses: Deep vein thrombosis, strokes.

MoA: Thrombolytic agent.

Dose: IV 3000–4000 U over 30 min > 1000 U/hr.

AE: Excessive bleeding, Bronchospasm, Flushing

Succimer

Uses: Lead, mercury and arsenic poisoning

MoA: Chelating agent – forms water-soluble salts

Dose: PO 350 mg/m^2/dose q8hr × 5 d > q12hr × 14 days

AE: Headache, Cramps, Flu-like illness

Succinylcholine

Uses: Neuromuscular block in anesthesia

MoA: blocks post-synaptic cholinergic receptors

Dose: IV 1–2 mg/kg (L) > 0.3–0.6 mg/kg q5–10 min

AE: Hypotension, Hyperkalemia, Bronchospasm

Sucralfate

Uses: Chronic gastritis, peptic ulcer

MoA: Cytoprotectant - coats gastric mucosa

Dose: PO 40–80 mg/kg/d q6hr (max 500 mg/dose)

AE: Constipation, Abdominal cramps

Sufentanyl

Uses: Pre-operative sedation, analgesia.

MoA: Narcotic (Opioid) analgesic

Dose: IV 10–25 mg/kg

AE: Hypotension, Respiratory depression, Vomiting

Tacrolimus

Uses: Steroid resistant/dependent/frequent relapser nephrotic syndrome, To prevent GVHD after organ transplant.

MoA: Immunosuppressant.

Dose: IV 0.05–0.1 mg/kg/d (Slow infusion), followed by > PO 0.1–0.3 mg/kg/d q12hr

AE: Hypertension, hyperglycemia, liver/renal toxicity

Note: Periodic drug level monitoring is advised.

Terbutaline

Uses: Asthma - Acute attack/status

MoA: Selective β_2 agonist (short-acting)

Dose: As per route of administration:

- MDI 250–500 µg/dose
- Nebulization: 2.5 mg/dose (5 mg above 20 kg)
- PO 0.05 mg/kg/dose q8hr (max 5 mg/dose)
- SC 0.005–0.01 mg/kg/dose q6–8hr, if required

AE: Same as with salbutamol

Terfenadine

Uses: Allergic conditions (Not <3 yr age).

MoA: Antihistamine - H_1 receptor antagonist.

Dose: PO 1 mg/kg/dose q24hr *or*
PO 15 mg q12hr (30 mg >12 yr)

AE: Mild sedation (less than other antihistamines)

Thiamine (Vitamin B_1)

Uses: Beriberi, Wernicke's encephalopathy

MoA: Nutritional supplement

Dose: IV/IM/PO 5–10 mg q24hr × 6 wk > 0.5–1.5 mg q24hr to prevent recurrence

AE: Rash, Parasthesia, Angioedema.

Thiopental

Uses: Anesthesia induction, intractable Status epilepticus

MoA: Barbiturate (Ultra-short acting).

Dose: As per indications:

- Anesthesia: IV 5–8 mg/kg/dose, repeat as needed.
- Status Epilepticus: IV 5–10 mg/kg (L) > 2–20 mg/kg/hr

AE: Hypotension, Bronchospasm, Respiratory depression

Tissue Plasminogen Activator (TPA)

Uses: Thrombolytic therapy.

MoA: Converts plasminogen to plasmin.

Dose: As per mode of administration:

- *Systemic:* IV 0.1–0.6 mg/kg/hr for 2–6 hours
- *Site-directed*: IV 0.1–0.3 mg/kg (L) >0.01–0.03 mg/kg/hr

AE: Bleeding, arrhythmia.

Note: Concomitant heparin therapy is necessary to avoid thromboembolic complications.

Tolazoline

Uses: Persistent pulmonary hypertension in newborns

MoA: α-adrenergic blocker.

Dose: IV 1–2 mg/kg (L) > 1–2 mg/kg/hr infusion.

AE: Hypotension, bleeding

Topiramate

Uses: Epilepsy (Add-on drug in complex seizures)

MoA: Carbonic anhydrase inhibitor

Dose: PO 1–3 mg/kg/d q12hr, increase gradually to 5–10 mg/kg/d

AE: Behavioral dysfunction, Suicidal tendencies

Tranexamic Acid

Uses: To reduce bleeding during dental treatment in hemophilia

MoA: Inhibits plasminogen activation

Dose: IV 10 mg/kg before surgery, then/or
PO 25 mg/kg/dose q6–8hr × 2–8 days

AE: Hypotension, Thromboembolic complications

Triamterene

Uses: Diuretic - Mild/moderate edema, Ascites, Hypertension

MoA: Aldosterone antagonist (Potassium-sparing).

Dose: PO 2–4 mg/kg/d q12–24hr.

AE: Hyperkalemia, Hyperchloremic acidosis.

Note: Avoid in renal failure.

Triclofos Sodium

Uses: Pre-procedure sedation

MoA: Melatonin agonist

Dose: PO 30–50 mg/kg/dose q12hr (max 100 mg/kg/dose)

AE: Rash, GIT upset

Trifluoperazine

Uses: Psychosis, Refractory anxiety (> 3 yrs of age)

MoA: Phenothiazine - blocks dopaminergic receptors.

Dose: PO 1–2 mg/d q6–12hr, (2–4 mg/d above 5 yrs age).

AE: Extrapyramidal reactions, Hypotension, Arrhythmia

Tubocurarine

Uses: Neuromuscular block in anaesthesia

MoA: Competitively blocks acetylcholine receptors

Dose: IV 0.2–0.5 mg/kg (L) > 0.04–0.1 mg/kg q15–25 min

AE: Hypotension, Respiratory depression

Urokinase

Uses: Thrombo-embolic episodes of recent onset.

MoA: Thrombolytic agent (Plasminogen > plasmin).

Dose: IV 4400 U/kg L > 4000–10000 U/kg/hr.

AE: Excessive bleeding, bronchospasm, flushing.

Ursodiol (Ursodeoxycholic Acid)

Uses: Neonatal cholestasis, Gall stones.

MoA: Decreases cholesterol content of bile.

Dose: 10–30 mg/kg/d q8–12hr.

AE: Diarrhea, Pruritis, Rhinitis.

Valproic Acid (Sodium Valproate)

Uses: Broad-spectrum anticonvulsant, Migraine >12 yr

MoA: Sodium channel inhibitor.

Dose: PO 15–20 mg/kg/d q8–12hr (max 60 mg/kg)

AE: Hepatitis, Irritability, Thrombocytopenia

Varicella Zoster Immunoglobulin (VZIG)

Use: High-risk Varicella exposure – (a) Immunocompromized children, (b) Newborns of mothers developing varicella 5 days before or 2 days after delivery, and (c) Postnatal exposure in preterm babies <28 weeks or <1 kg.

MoA: Passive prophylaxis, within 48 hrs of exposure (max 96 hr)

Dose: IM 125 U/10 kg body weight (max 625 U)

AE: Local pain, hypersensitivity

Vasopressin (ADH)

Uses: Refractory shock, Diabetes insipidus, Bleeding from esopahgeal varices.

MoA: Hormone replacement, peripheral vasoconstriction

Dose: As per indications:

- *Refractory shock:* IV 0.01–0.03 U/kg/min
- *D. insipidus:* SC/IM 2.5–10 U/d q6–12hr
- *GIT bleeding:* IV 20 U over 15 min > 0.2–0.8 U/1.73 m^2/min

AE: Hypertension, Water intoxication.

Vecuronium

Uses: Neuromuscular blocking agent in anesthesia.

MoA: Competitively blocks acetylcholine receptors

Dose: IV 0.05–0.1 mg/kg q1hr as needed.

AE: Tachycardia, Hypotension, Flushing

Verapamil

Uses: Hypertension, Arrhythmia

MoA: Calcium-channel blocker.

Dose: As per indications - (Not for use <1 yr).

- Arrhythmia: IV 0.1–0.3 mg/kg/dose slowly, repeat after 20 min
- Hypertension: PO 4–8 mg/kg/d q6–8hr.

AE: Heart blocks, Hypotension

Note: Contraindicated in cardiogenic shock, severe CCF.

Vigabatrin

Uses: Infantile spasm, Add-on drug in refractory seizures.

MoA: Binds GABA receptors to increase neuroinhibitory GABA levels

Dose: PO 40–150 mg/kg/d q12–24hr (start with lower dose)

AE: Hyperactivity, Weight gain, Optic nerve damage

Vitamin A (Retinol)

Uses: Treatment and Prevention of Vit A Deficiency

MoA: Nutritional supplement

Dose: As per WHO schedule:

- *Treatment:* Three age-wise doses on day 1, 2, 14* PO 50000 IU (<6 mo), 1,00,000 IU (6–12 mo), 2,00,000 IU (>12 mo)
  (*Or IM with half of the oral dose).*
- *Prophylaxis*: PO 1,00,000 IU at 9 mo > 2,00,000 IU every 6 mo till 5 years

AE: Pseudotumor cerebri, Hypervitaminosis A

Vitamin C (Ascorbic Acid)

Uses: Scurvy, Urinary acidification (in poisonings)

MoA: Nutritional supplement, urine acidifier

Dose: As per indications:

- *Scurvy:* PO/IV 200–500 mg/d 12–24hr till recovery, then PO 100 mg/d × 3 months to prevent recurrence
- *Urine Acidifier:* PO 500 mg/dose q6hr

AE: Renal stones on prolonged use in high doses

Vitamin D_3 (Cholecalciferol)

Uses: Treatment and prevention of Rickets

MoA: Nutritional supplement

Dose: As per IAP recommendations -

- Treatment: PO 3000 IU (2000 IU < 1yr) q24h × 12 wk, then
  PO 400–600 IU q24hr as maintenance (with calcium)
  Or PO 60,000 IU every 2 weeks × 5 doses
- Prevention: 400 IU in infants and high-risk children

AE: Hypervitaminosis D, Hypercalcemia

Vitamin D (Calcitriol)

Uses: Vitamin D resistant/dependent rickets

MoA: Activated Vit D analog (1,25 Dihydroxy-cholecalciferol)

Dose: IM/PO 0.5–2 µg q24h (0.25–0.75 µg <5 yr) increase by 0.005–0.01 µg/kg monthly to response

AE: Hypervitaminosis D, Hypercalcemia

Vitamin D_2 (Ergocalciferol)

Uses: Renal rickets/osteodystrophy

MoA: Vit D_2 (2000 times less potent than D_3)

Dose: PO 25,000–2,50,000 IU/kg/d.

AE: Hypervitaminosis D, Hypercalcemia

Vitamin E (α-Tocoferol)

Uses: Preterms, Hemolytic anemia, Chronic liver disease

MoA: Anti-oxidant, Nutritional supplement

Dose: PO 5–25 IU q24hr (max 400 IU)

AE: None significant

Vitamin K_1 (Phytonandione)

Uses: Vit K deficiency, e.g. Hemorrhagic disease of newborn, chronic liver disease, etc

MoA: Synthesis of some clotting factors

Dose:

- *Treatment* (in bleeding): IM/IV/PO 5 mg > preventive doses
- *Prevention:* IM/PO 1 mg at birth or periodically in chronic liver disease

Note: Menandione (K_3) - A synthetic, water-soluble preparation is preferred for oral supplement in chronic liver disease, as it does

not require bile salts for absorption. However, it is ineffective to control anticoagulant -induced bleeding and should not be used in newborns or G6PD deficiency, due to risk of hemolysis.

Warfarin

Uses: Oral Anticoagulant.

MoA: Prevents hepatic synthesis of Vitamin K-dependent clotting factors

Dose: PO 0.1–0.2 mg/kg q24 hr (titrate to INR 2–3).

AE: Excessive bleeding

Zinc

Uses: Zinc deficiency, Acrodermatitis entropathica

MoA: Nutritional supplement

Dose: As per indications:

- Treatment: PO 1–3 mg/kg/d q12hr × 2–4 wks
- Prevention in Diarrhea (WHO):
  PO 10 mg/kg q24hr (2–6 mo) > PO 20 mg/kg q24hr (6 mo–5 yr)

AE: Overdose may cause Copper deficiency

Index

A

Abdominal
  distension 382
  mass/lump 382
  migraine 378
  pain 378
    acute 378, 379
    recurrent 378, 379
      functional 378
      functional vs organic 379
  trauma 813
Abdominocentesis 883
Abetalipoproteinemia 285, 409
ABO-hemolytic disease (ABO-HDN) 340
Absence seizures 547
Acetabular index 723
Achalasia 387
Acheiria 721
Achondroplasia 729
Acid-base balance, normal 123
Acid-base disorders 123
  evaluation 124
  pathophysiology 124
Acne vulgaris 773
Acro/oxycephaly 720
Acrocyanosis 312
Acrodermatitis enteropathica 111, 409
Acromegaly 693
Acromelia 729
ACTH challenge test 702
Acute adrenal insufficiency 703
Acute cortical necrosis 674
Acute encephalitis syndrome 569
Acute epiglottitis 449
Acute flaccid paralysis (AFP)
  case classification 217
  differential diagnosis 216
  surveillance 216, 586
Acute hepatic failure 422
  causes 422
  clinical features 422
  management 423
Acute inflammatory demyelinating polyneuropathy 588
Acute intermittent porphyria 290
Acute interstitial nephritis 680
Acute intestinal obstruction 409
Acute kidney injury 671
  in newborns 674
Acute life-threatening events 828
Acute lymphoblastic leukemia 639
Acute phase proteins 133
Acute respiratory distress syndrome 801
  Berlin criteria 802
Acute respiratory failure 799
  ABG analysis 800
Acute tonsillopharyngitis 445
Acute transverse myelitis 583
Acute tubular necrosis 680
Adactylia 721
Adaptive immune response, physiology 134
Adaptive immunity 131
Addison disease 703
Adenoidal hypertrophy 447
Adenoma sebaceum 579
Adenovirus infections 229
Adolescence
  behavioural changes 364
  common health problems 365
  psychosocial problems 368
Adolescent
  bunions 725
  friendly health clinics 836
  friendly health services 370
  growth 363
  health check-up 369
Adrenal crisis, *see* Acute adrenal insufficiency
Adrenocortical insufficiency 701
Adrenogenital syndrome 705
Adrenoleukodystrophies 582
Adverse events following immunization 165
  causality assessment 166
  classification 165
  definition 165
  reporting 166
Aerosol
  devices 456
  therapy 455
Alacrima 778
Alagille syndrome 273
Albinism 282, 761
Albright hereditary osteodystrophy, *see* Pseudohypoparathyroidism
Aldehyde test 253
Alkaptonuria 283
Allens's test 871
Allergic
  bronchopulmonary aspergillosis 465
  conjunctivitis 779
  rhinitis 443
Alopecia 773
α-fetoprotein 296
Alport's syndrome 664, 720
Amaurosis 786
Ambiguous genitalia 706
Amblyopia 787
Amebiasis 255
  amebic liver abscess 255
  extraintestinal 255
  intestinal 255
  management 255
Amelia 721
Amenorrhea in adolescents 366
Ametropia 787
Amniotic band disruption sequence 361
Amniotic constriction bands 721, 753
Amylase rich foods 96
Anaerobic infections 207
  clinical spectrum 207
  risk factors 207
Anal fissures 411
Anaphylaxis 142
  clinical presentation 142
  management 143
  precipitating agents 142
Anatomy of
  bones 719
  gastrointestinal tract 372
  kidney 653
  liver 416
  respiratory tract 430
  skin 752
Anderson disease 288
Anemia 599
  acquired pure red cell 615
  aplastic 614
    acquired 614
    constitutional 614
  autoimmune hemolytic 614
  congenital dyserythropoietic 616
  etiological classification 599
  G6PD deficiency 608
  in chronic diseases 615
  in newborn 357
  iron deficiency 602
  juvenile pernicious 103, 606
  megaloblastic 605
  morphological classification 600
  physiological, of infancy 602
Anemia Mukt Bharat 605
Anencephaly 558
Aneuploidy 266
Aneurysmal bone cyst 736
Angioneurotic edema 764
Angle sign 105
Anhidrosis 774
Anhidrotic ectodermal dysplasia 754
Anion gap 125
Aniridia 782
Anisometropia 788
Ankylostomiasis 258
Anorectal malformations
  classification 394
  embryogenesis 394
Anorexia nervosa 368
Antalgic gait 728
Antenatal care 294
Anterior horn cell disorders 587
Anthropometric assessment 84
Anthropometric indicators 7
Antiarrhythmic agents 521
Anticonvulsant drugs 544
Antihypertensive drugs, 526
Anti-nuclear antibodies 738
Anti-oxidants 68, 112
Anti-snake venom 818
Aortic regurgitation 513
Aortic stenosis 500
Apgar scoring 304
Aphthous ulcers 384
Aplasia cutis congenital 753
Aplastic crises 613

Apnea
  primary 300
  terminal 300
Apnea of prematurity 337
Apnea test 810
Appendicitis, acute 410
Appetite test 91
Apt and Downey test 356
Aqueduct stenosis 561
Arnold-Chiari malformation 561
Arrhythmia 519
Artemisinin combination therapy 249
Arterial ischemic strokes 551
Arthritis
  acute 733
  chronic 742
  enthesitis-related 741
  juvenile idiopathic 739
    diagnostic criteria 741
    etiopathogenesis 739
    ILAR classification 739
    laboratory diagnosis 741
    management 742
    sub-types 740
  poststreptococcal reactive 179
  psoriatic 741
  reactive 733
  rheumatic 509
  septic 732
Arthrogryposis multiplex congenital 722
Artificial immunity 144
Ascariasis 256
Ascites 414
Ash-leaf macules 579
Askin tumor 649
Ask-upmark kidney 659
Asperger's disorder 50
Aspergillosis 244
Aspiration pneumonia 464
Assessment of vision in children 786
Assignment of sex of rearing 708
Assman's focus 191
Asthma, bronchial 452
  anti-asthmatic medications 455, 456
  asthma symptom control classification 459
  clinical manifestations 453
  clinical variants 454
  diagnosis 454
  difficult to control asthma 460
  etiopathogenesis 452
  management 455
  management, step-wise 458
  pathophysiology 453,454
  step-wise pharmacotherapy 459
Asthmatic exacerbation, acute 454
  emergency management 457
  severity assessment 458
Astigmatism 788
Astrocytoma, cerebellar 577
Ataxia 554
  acute cerebellar 555
  Friedreich 582
  hysterical 555
  recurrent 555
  telangiectasia 577, 580
Atelectasis 471
Athetosis 556
Atlanto-axial joint instability 726
Atonic seizures 549
Atrial
  complexes, premature 519
  fibrillation 520
  flutter 520
Atrial septal defects 499
    course and complications 500
    hemodynamics 499
    management 500
Atrioventricular blocks 521
Attention deficit hyperactivity disorder 52
    diagnostic criteria 54
Auspitz sign 768
Austin flint murmur 486
Autistic spectrum disorders 50
  diagnostic criteria 51
  screening guidelines 50
Autoimmune hepatitis 426
Autoimmune polyglandular endocrinopathies 697
Autonomic bladder 531
Autonomic storm 818
Autosomal dominant (AD) disorders 267
Autosomal recessive (AR) disorders 267

B

Babinski sign 530
Baby friendly hospital initiative 76
Back pain 727
Back-blows and chest-thrust maneuver 793
Bacterial conjunctivitis 779
Bacterial tracheitis 450
Bag and mask ventilation 797
Balanced diet 80
Ballismus 556
Bangle test 85
Banti syndrome 632
Barlow test 722
Baroda development screening test 23
Barr body 270
Bartter syndrome 679
Basic life-support 790
  algorithm 791
Bayley scale of infant development 42
B-cell disorders 136
BCG lymphadenitis 148
BCG vaccine 147
BCGiosis 148
Becker muscular dystrophy 592
Beckwith-Wiedemann syndrome 647
Behçet's disease 746
Bell palsy 590
Bell tympany, *see* Coin test
Benedict test 656
Benign myoclonus in newborn 355
Benign myoclonus of infancy 548
Benign rolandic epilepsy 549
Benzidine test 656
Berger disease, *see* IgA nephropathy
Beriberi 101
Bernard-Soulier syndrome 625
β-thalassemia 609
Bezoars 390
Bilirubin metabolism 337
Biomedical waste disposal 261
Biopsy, liver 881
Biopsy, renal 882
Biot's breathing 433
Biotin deficiency 104
Biotinidase deficiency 285
Birbeck granules 650
Birth asphyxia 316
  diagnostic criteria 316
  multi-organ dysfunction in 317
  pathophysiology 316
Bitot' s spot 99
Bladder exstrophy 682
Blalock-Taussig shunt
Bleeding neonate 355
  causes of 356
  diagnostic approach 356
Blepharitis 777
Blepharospasm 777
Blind loop syndrome 409
Blindness 786
Blood pressure 482, 858
Blood transfusion set 872
Blood-product transfusions 629
  complications 630
  guidelines
  plasma transfusions 630
  platelet transfusions 630
  RBC transfusion 629
Bloom syndrome 273, 765
Body
  fluids 115
  proportions 9, 860
  surface area nomogram 888
Body mass index 8, 860
Bone age
  advanced 10
  assessment 10
  delayed 10
Bone marrow aspiration 880
Bone marrow aspiration needle 880
Bone masses 735
  bone-in-bone appearance 731
Bornholm disease, *see* Pleurodynia
Botulism 206
Bowing, physiological 723
Bow-legs, *see* Genu varum
BP instrument and cuffs 887
Brachial plexus injuries 319
Brachycephaly 720
Brachydactyly 721
Brain abscess 573
Brain death 809
  criteria for death 810
Brain herniation, signs of 538
  brain injury, clinical indicators of 812
Branchial clefts, sinuses or cysts 753
Breakthrough varicella 212
Breast
  abscess 73
  crawl 71
  engorgement 73
  masses in adolescents 366
Breast milk
    composition 69
    jaundice 340
    stools 313
Breastfeeding
  advantages 69
  antenatal preparation and counselling 71
  in special situations 74

medications in lactating mothers 75
positions 72
signs of effective sucking 72
signs of good attachment 72
signs of good position 72
Breath-holding spells 63
Breech deformation sequence 361
Brittle diabetes 715
Brodie's abscess 732
Broke procedure 505
Bromhidrosis 774
Bronchiectasis 466
Bronchiolitis obliterans 452
Bronchiolitis, acute 451
Bronchitis, acute 452
Bronchitis, chronic 452
Bronchogenic cysts 471
Bronchopulmonary dysplasia 336
Bronchoscopy 438
Brucellosis 189
Brudzinski's sign 528, 565
Brush-field spots 782
Bruton agammaglobulinemia 136
Bruxism 60
Budd-Chiari syndrome 429
Bulimia nervosa 368
Bull's eye sign 410
Burns and scalds 814
classification 814
percentage burn in children 814
Burping 73
Butterfly rash 743

C

Café-au-lait spots 577, 760
Calcium 120
homeostasis 120
recommended dietary allowance 120
sources 120
Candidiasis 243
chronic mucocutaneous 137
clinical spectrum 243
cutaneous 758
diagnosis 243
high-risk factors 243
treatment 243
Cannulation
arterial 871
central venous 871
intraosseous 870
peripheral venous 868
Canthal index 721
Caput succedaneum 319
Carbohydrates 68
Carbuncle 756
Cardiac
arrest in children
management algorithm 798
catheterization 490
cycle 479
examination 483
magnetic resonance imaging 490
tamponade 522
Cardiomegaly 486
Cardiomyopathy
dilated 517
hypertrophic 518
restrictive 518
Cardiopulmonary resuscitation 790
Cardio-thoracic ratio 486
Carey Coombs murmur 486
Carnitine deficiency 285
Caroli disease 428
Carpenter syndrome 720
Carpopedal spasm 122
Casts 657
Cataplexy 551
Cataract 783
Cat-eye reflex 784
Catheterization, umbilical vein 870
Cavernous hemangiomas 755
Celiac disease 405
Cell-mediated immunity 131
Cellulitis 756
orbital 777
Centor criteria 446
Central venous cannulation 806
Cephalohematoma 319
Cerebral gigantism 41, 693
Cerebral malaria 572
diagnostic criteria, WHO 573
treatment 573
Cerebral palsy 563
clinical types
ataxic 564
atonic 564
spastic 563
extrapyramidal 564
early indicators 564
etiology 563
management 564
Cerebral sinovenous thrombosis 552
Cerebrospinal fluid (CSF)
examination 532
physiology of CSF formation 560
straw-color CSF 568
Cerebrovascular strokes 551
Cervical lymph nodes, anatomy of 634
Cervical ribs 727
Chaddock's sign 530
Chalazion 777
Charcot-Marie-Tooth disease 589
Charge association 361
Chédiak-Higashi syndrome 136
Cheilitis 384
Chelation therapy 611
Chemical conjunctivitis 779
Chenye-stokes breathing 433
Cherry-red epiglottis 449
Cherry-red spot 784
Chest circumference 9
Chest compressions 791
two-finger technique 792
two-thumb technique 792
two-hand technique 791
Chest pain 442, 481
Chest wall injuries 813
Chickenpox 212
clinical presentation 212
complications 213
hemorrhagic 213
neonatal 213
pathogenesis 212
prevention 213
Chikungunya 221
Child
abuse and neglect 838
behaviour, determinants 56
development units 43
guidance clinic 65
health
current status 3
determinants 2
indicators, India 829, 830
interventional strategies 3
labour 839
mortality rate 832
CHILD syndrome 469
Childhood primary angiitis of central nervous systems 553
Childhood undernutrition 86
classifications 90
clinical spectrum 87
complications 90
diagnostic assessment 89
etiopathogenesis 86
management 91
prevention 97
Chlamydial infections 244
Chloride-loosing enteropathy 409
Choanal atresia 443
Cholecystitis, acute 413
Choledochal cysts 413
Cholelithiasis 413
Cholera 188
Cholera vaccine 156
Chondrodysplasias 728
Chorea 556
Chorea, benign hereditary 556
Chorioretinitis 781
Christmas disease 625
Chromium deficiency 112
Chromosomal disorders 269
clinical indicators 269
Chronic bullous disease of childhood 767
Chronic diarrhea 404
causes 404
Chronic gastritis 390
Chronic granulomatous disease of childhood 136
Chronic kidney disease 675
KDIGO classification 675
management 676
NKF-KDOQI classification 675
pathogenesis 675
severity 675
Chronic liver disease 424
causes 424
clinical indicators 424
management 425
Chronic myelogenous leukemia 643
adult 643
juvenile 643
Chronic tonsillitis 446
Chylothorax 475
Circumcision 689
Clasp-knife spasticity 530
Clavicular fractures in newborns 320
Claw sign 410
Cleft lip 382
Cleft palate 382
Clinodactyly 721
Clitoral hypertrophy 865

Clotting time 621
Clouston syndrome 754
Clubbing 483, 859
Coagulation
  cascade 619
  disorders 625
  factors 619
Coarctation of aorta 501
Cobalamin (B12) deficiency 103
Cockayne syndrome 765
Cog-wheel rigidity 530
Coin test 435
Cold chain system 164
Cold-chain equipment 164
Collodion baby 755
Coloboma of iris 782
Colostrum 69
Comatose child 534
  causes of 535
  diagnostic evaluation 535
  management 536
Combination vaccines 158
Comedones 774
Commando-crawl 563
Common cold, *see* Acute rhinitis
Common variable immunodeficiency disorder 137
Complement disorders 136
Complement system 132
Complementary feeding 78
  characteristics 79
  principles 79
Complete blood count 598
Complete heart block 522
Condom catheter 886
Congenital
  adrenal hyperplasia 702
    neonatal screening 702
    prenatal diagnosis 702
  asplenia 634
  dacryostenosis 778
  giant pigmented nevi 761
  hepatic fibrosis 428
  hydronephrosis 659
  malformations 360
    classification 360
    causes 360
    diagnostic clues 361
  megacolon, *see* Hirschprung's disease
  muscular dystrophies 593
  pure red cell aplasia 615
  rubella syndrome 211, 350
  scoliosis 727
  syphilis 352
  toxoplasmosis 352
  varicella syndrome 213
Congestive cardiac failure 490
  causes 491
  clinical manifestations 491
  indicators in infancy 492
  management 492
  pathogenesis 490
  resistant 494
  severity assessment 492
Consanguinity 275
Constipation in newborn 314
Constipation, functional 380
Continuous kidney replacement therapy 674
Conversion disorder 64
Cooley's anemia 610
Coomb test 614
Copper 112
  deficiency 112
  toxicity 112
Cord clamping
  delayed 299
  early 299
Corneal
  opacities 781
  reflex 529
  reflex test 788
Cornelia de lange syndrome 721
Corpus callosum, agenesis of 560
Cortical thumb 564
Cough remedies 440
Cough, recurrent or persistent 438
Counseling
  developmental delay 43
  failure to thrive 34
  parents of serious/terminally ill child 809
Cour en sabot appearance 504
Cover test 788
COVID vaccines 157
COVID-19 infection 225
  diagnosis 225
  management 226
  pathogenesis 225
Cow-milk protein allergy 406
Cradle cap 769
Cranio-cerebral trauma 811
Craniopharyngioma 577
Craniosynostosis 720
Cretinism, endemic 698
  myxedematous type 698
  neurological type 698
Cri-du-chat syndrome 272
Crigler-Najjar syndrome 341
Crohn disease 406
Croup 449
Crouzon syndrome 720
Crown-to-rump vs rump-to-heel ratio (CR:RH ratio) 9
Cry in newborn 314
Cryptococcosis 244
Cryptorchidism 688
Cullen sign 374
Cushing disease 703
Cushing syndrome 703
Cutis laxa 755
Cyanosis 482
  causes 483
  clinical types
    central 483
    differential 483
    peripheral 483
Cyanotic or anoxic spells 504
  complications 504
  management 504
Cyclic neutropenia 136
Cystic adenomatous malformation, congenital 470
Cystic fibrosis 468
  diagnosis 468
  pathogenesis 468
Cystic hygroma 636
Cystinosis 679
Cytokines 132
Cytomegalovirus disease 225
  perinatal 351

D

Dacryoadenitis 778
Dancing eye-Dancing feet syndrome 646
Dandy-Walker malformation 561
Dawn phenomenon 715
Death criteria 809
Decerebrate posture 530
Decorticate posture 529
Deep tendon reflexes 530
  grading 530
Defibrillation 793
Dehydration 116, 860
  causes 117
  hypernatremic dehydration 117
  hyponatremic dehydration 116
  isonatremic dehydration 116
  severity assessment 117
Dehydration fever 314
Delee's mucus extractor 873
Delirium 537
Delivery room care 298
Demographic profile of India 829
Dengue 218
  case definitions 220
  clinical case classification 220
  clinical spectrum 218
  diagnosis 219
  epidemiology 218
  etiopathogenesis 218
  expanded dengue syndrome 219
  fluid replacement therapy 220
  hemorrhagic fever (DHS) 219
  management 219
  prevention 221
  shock-like syndrome (DSS) 219
  warning symptoms and signs 219
Dengue vaccine 157
Dengvaxia 221
Dennie's lines 443
Dennie-Morgan folds 443
Dennis-Brown splint 724
Dental caries 383
Dentition, delayed 10
Dentition, normal 9
Denver development screening test 23
Denys-Drash syndrome 647
Dermatitis herpetiformis 768
Dermatitis, atopic 770
Dermatitis, contact 771
  allergic 771
  irritant 771
Dermatitis, seborrheic 769
Dermatomyositis, juvenile 745
Dermatophytoses 758
Development 5, 18
  assessment 21
  assessment kit 22
  assessment tests 42
  delay 41
  deviance 41
  dissociation 41
  laws of 18
  milestones 19
  quotient 41

regression 41
screening 23
screening, IAP guidelines 42
surveillance 21
Developmental dysplasia of hip 722
Dexamethasone suppression test 704
Diabetes
insipidus 694
central 694
nephrogenic 694
insipidus, nephrogenic 680
mellitus 710
mellitus, maturity onset 715
mellitus, type I 711
diagnosis 712
diagnostic criteria 711
etiopathogenesis 711
insulin dose modifications 714
insulin therapy 713
late complications 715
management 712
monitoring 714
pathophysiology 711
mellitus, type II 715
Diabetic coma 711
Diabetic ketoacidosis 711
diagnostic criteria 712
management 712
pathophysiology 712
Diamond-Blackfan syndrome 615
Diaphragmatic hernia 387
Diaphragmatic paralysis 336
Diarrhea
acute 396
antimicrobial therapy 400
anti-secretory agents 401
causes 396
diagnostic assessment 397
fluid replacement therapy, WHO guidelines 398
nutritional management 401
pathogenesis 396
pathophysiology 397
probiotics and prebiotics 400
zinc supplementation 400
in newborn 313
persistent 401
dietary plan 402
etiopathogenesis 401
micronutrient supplementation 403
risk-factors 402
Diarrrhea treatment and training units 401
Diastematomyelia 584
Dietary assessment 84
Dietel's crisis 380
DiGeorge syndrome 137, 272, 700
Digitalization in children 493
Digoxin toxicity 493
Dine's formula 8
Diphtheria 180
clinical features 181
complications 181
diagnosis 181
management 182
prevention 182
Diplopia 787
Dipstick 656
Disaccharide (lactose) intolerance 403
Disorders of sex development 706
Disorders of sex-steroids 705
Disseminated intravascular coagulation 627
Dog bite, management 231
active immunization 232
local wound care 231
passive immunization 231
post-exposure prophylaxis 232
re-exposure prophylaxis 232
WHO categories 231
Doll's eye maneuver 529
Double-bubble sign 391
Double-track sign 390
Doughnut sign 410
Down syndrome 270
clinical phenotype 270
cytogenetics 270
genetic counselling 271
parental counselling 272
periodic screening 271
prenatal screening 272
recurrence risk 271
Dravet syndrome 547
Drip and drop method 97
Dripping candle appearance 579
Drowning and near drowning 815
Drug dyskinesia 551
Drug fever 177
Drug-induced lupus 745
Drugs and medications 888
antibiotics 888
anti-fungal agents 896
anti-malarial agents 896
anti-parasitic agents 897
anti-protozoal 897
anti-tubercular agents 893
anti-viral agents 894
general medications 899
Dry powder inhalers 877
Dry-eye, *see* Alacrima
DT vaccine 149
DTaP vaccines 149
DTwP 148
Duchenne muscular dystrophy 591
Duhamel's pull-through operation 394
Duke criteria 515
Duodenal atresia 391
Dyscalculia 45
Dyscoria or corectopia 782
Dysentery, causes of 186
Dysgraphia 45
Dyslexia 45
Dysmenorrhea 366
Dysphagia 376
Dyspnea 480
New York Heart Association (NYHA) grades 480
Dystonia 555
Dystonia musculorum deformans 583

E

Earache, *see* Otalgia
Early childhood development 18
Early neonatal mortality rate 293
Eaton agent 245
Ebstein anomaly 506
Echocardiography 489
Ectodermal dysplasia 753
Ectopia lentis 783
Ectopic pelvic kidneys 659
Ectropion 777
Eczema 770
Eczema, dyshidrotic 771
Edema 116, 312, 859
causes 116
diagnostic approach 116
pulmonary 472
Edrophonium (tensilon) test 590
Edward syndrome 272
EEC syndrome 754
Egg on string appearance 505
Ehlers-Danlos syndrome 755
Electrocardiography 487
Electrophysiological studies 534
Elephant man *see* Proteus syndrome
Embryology
tracheo-esophageal fistula 385
Embryogenesis, Anorectal malformations 394
Embryogenesis, lungs 430
Embryology of
anorectal malformations 394
bones 719
brain 557
cleft lip and cleft palate 382
diaphragmatic hernia 388
gastrointestinal tract 372
heart 477
Hirschprung's disease
kidney 653
liver 416
lungs 430
skin 751
tracheo-esophageal fistula 385
urinary tract 680
Emphysema 472
Empyema thoracis 473
Encephalitis 569
anti-n-methyl-d-aspartate receptor (ANMDAR) 571
autoimmune 571
herpes 571
Japanese 570
Rasmussen 572
viral 569
Encephalocele 558
Encephalomyelitis, acute disseminated 571
Encephalopathy 569
Enchondroma 736
Encopresis 59
diagnostic criteria 60
Endocardial fibroelastosis 519
Endotracheal tube 875
Endotracheal intubation 796, 875
End-stage renal disease 675
Energy 67
Enophthalmos 776
Enteric fever 183
carrier state 185
complications 184
diagnosis 184
management 185
pathogenesis 184
prevention 185
Enterobiasis 257
Enteroviral infections 217
clinical spectrum 217
Entropion 777
Enuresis 58

Enuresis, diagnostic criteria (DSM-V) 58
Enuresis, primary 59
Enuresis, secondary 59
Enzyme replacement therapy 277
Eosinopenia 618
Eosinophilia 618
Eosinophilic granuloma 650
Ephelides or freckles 761
Epicanthic folds 778
Epidermolysis bullosa 768
Epididymo-orchitis 690
Epilepsy 541
Epilepsy syndromes 547
Epileptic encephalopathy 547
Epileptic spasms 542
Episcleritis 780
Epispadias 683
Epistaxis 444
Epstein pearls 313
Epstein-Barr virus 224
Equinus gait 728
Erb-Duchenne paralysis 319
Erysipelas 756
Erythema
  infectiosum 211
  marginatum 509
  multiforme 767
  nodosum 772
  toxicum 312
Erythroblastosis fetalis 339
Erythrocytic protoporphyria 291
Erythropoiesis 597
Erythropoietin 632
Esbach's method 656
Esophagitis 387
Evening colic 57, 314
Eventration 388
Ewing sarcoma 649
Ewing's family 649
Examination of a newborn 304
Examination, abdomen 373
Examination, respiratory system 434
Exanthem subitum, *see* Roseola infantum
Exanthematous fevers 175
Exchange transfusion 342
Exophthlamos 776
Expressed breast milk 77
Expressivity 265
Extended neonatal mortality rate 293
Extensor plantar response 530
Extra-corporeal membrane oxygenation 801
Extra-hepatic biliary atresia 345
Extrasystoles 519

F

F-100 diet 94
F-75 diet 94
Fabry disease 287
Face-mask 874
Facioscapulohumeral dystrophy 593
Failure to thrive 34
  causes 34
  diagnostic approach 35
  management 35
  parental counseling
  trial feeding 35
Fallot physiology 503
Fanconi syndrome 679
Fanconi-Bickel syndrome 288
Farber disease 287
Fats 67
Febrile neutropenia 176
  management 177
  risk-stratification 177
  severity 176
Febrile seizures 545
  prophylaxis 546
  simple *vs* complex 546
Female pseudohermaphroditism 707
Fetal
  circulation 478
  distress 296
  growth chart 321
  monitoring 294
  therapy 296
  to neonatal transition 478
Fetal hydantoin syndrome 721
Fever in children 172
  diagnostic considerations 173
  management 174
  prolonged fever 173
  with localizing signs 172
  without focus 172
  in neutropenic child *see* febrile neutropenia
  with purpura *see* hemorrhagic fevers
  with rash *see* exanthematous fevers
Fibers 68
Fibrinolytic system 620
FIGLU test 103, 606
Figure of 8 appearance 506
Filariasis 254
Finger pulse oximeter 887
Finger-to-nose test 530
Fixed drug eruption 763
Flat foot, *see* Pes planus
Flatus tube 885
Floppy infant 594
  cause of 595
  signs of floppiness 594
Fluorine 111
Fluorine deficiency 112
Fluorosis 112
Flush method 525
Foam test 656
Focal (partial) seizures 549
Foley's catheter 885
Folic acid deficiency 103, 605
Folic acid deficiency in pregnancy 103
Folliculitis 756
Food allergy 406
Food pyramid 81
Fore milk 69
Foreign bodies in airways 450
Foreign bodies, pharyngeal 447
Foreign body accidents 816
  bronchial foreign bodies 816
  ear foreign bodies 816
  esophageal foreign bodies 816
  nasal foreign bodies 816
  pharyngeal foreign bodies 816
Foreign body airway obstruction 793
Foreign body in ears 449
Foreign body, esophagus 387
Fouchet test 656
Fractures in childhood 736
Fragile X syndrome 274
Free radical tissue injury 112
Free radicals 112
Frog-like posture 530
Frog-like posture 594
Fukuyama disease 593
Funnel chest *see* Pectus excavatum
Furuncle 756
Fussy infant 56

G

G6PD deficiency anemia 608
Galactagogues 74
Galactokinase deficiency 289
Galactosemia 288
Galeazzi sign 722
Gallstone, *see* Cholelithiasis
Ganglion 736
Gangliosidoses 582
Gangliosidoses, juvenile or adult GM2 582
Gas gangrene 207
Gastro-colic reflex 313
Gastroesophageal reflux disease 386
Gastroschisis 395
Gaucher disease 286
Gene therapy 277
General physical examination 856
  characteristic facial features 862
  common head abnormalities 861
  general appearance 857
  general considerations 856
  general markers 858
  head-to-toe examination 860
  vital signs 857
Generalized epilepsy with febrile seizure plus 547
Generalized tonic-clonic seizures 547
Genetic counseling 278
Genetic disorders
  evaluation 275
  indicators 275
  laboratory evaluation 275
  management 277
Genome 264
Genomic imprinting 269
Genotype 265
Genu recurvatum 724
Genu valgum (knock-knee) 723
Genu varum 724
Gerhardt test 656
Ghon lesion 190
Gianotti-Crosti syndrome 770
Giardiasis 255
Gigantism 693
Giggling incontinence 59
Gilles De La Tourette syndrome 61
Girl child 839
GIT bleeding 381
Glanzmann thrombasthenia 625
Glaucoma 782
Gliomas 577
Global alliance for vaccine and immunization 163
Glomerular filtration rate 658
Glomerulonephritis
  acute 662
  acute post-infectious 662
  acute post-streptococcal 662

chronic 663
membranoproliferative 663
rapidly progressive 663
Glycogen storage disorders 287
Gmelin test 656
Goiter 697
congenital 697
endemic 697,698
puberty 697
sporadic 697
Gomez recovery syndrome 95
Gonadotropins 706
Goodpasture disease 664
Gordon's method 530
Gower sign 592
Graft versus host disease 631
Graham Steell's murmur 486
Graulocyte stimulating factors 632
Graves' disease 699
Gray platelet syndrome 625
Greulich-Pyle atlas 10
Ground-glass appearance 105
Growing pains 726
Growth 5
assessment, IAP recommendations 13
charts 11
charts, IAP 29-32
charts, WHO 25-28
curve 15
determinants 5
hormone deficiency 692
diagnostic criteria 693
hormone therapy 693
laws 6
monitoring and promotion 15
norms, reference 11
norms, standard 11
norms, WHO vs IAP 11
patterns 6
phases or periods 6
velocity 15
Guillain-Barré syndrome 588
Gynecomastia in adolescents 366

H

H. influenzae B (Hib) vaccine 152
H. influenzae B disease 186
clinical spectrum 187
prevention 187
Hackett's classification 633
Haemorrhage, fetomaternal 357
Haemorrhage, subconjunctival 313
Hair end-on appearance 610
Hallevorden Spatz disease 583
Halls criteria 271
Hallux valgus deformity, *see* Adolescent bunions
Hammer toe 722
Hand-foot-mouth disease 217
Handicapped child 840
Hand-Schüller-Christian disease 650
Handwashing 261
Hanifin and Rajka criteria 770
Harlequin color change 312
Harlequin fetus 755
Hartnup disease 283
Hashimoto's thyroiditis 697
Hay's sulfer test 656
Hb-M disease 609
Head circumference 8, 13
Head holding 23
Head injury
diagnostic evaluation 812
general management 812
Headache 539
intracranial or traction 539
migraine 540
diagnostic criteria 540
ophthalmic 540
sinus 540
tension 539
Head-tilt-chin-lift maneuver 792
Healthy plate 81
Hearing assessment, IAP guidelines 48
Hearing loss 47
Heat
coagulation test 656
cramps 819
edema 819
exhaustion 819
injuries 819
stroke 819
syncope 819
tetany 819
HEEADSSS 369
Heel puncture 872
Heel-to-shin test 530
Heimlich maneuver 793
Helicobacter pylori 390
Heliotrope eyelids 745
Heliox ventilation 801
Hematopoiesis, physiology of 597
Hematopoietic growth factors 632
Hematopoietic stem-cell transplantation 631
Hematuria 660
benign familial 664
causes 660
diagnostic approach 661
glomerular vs non-glomerular 661
Hemiballismus 556
Hemihypertrophy, congenital 721
Hemimelia 721
Hemiplegia 553
acute, of childhood 553
chronic progressive 553
clinical localization of lesions 554
diagnostic approach 553
recurrent or alternating 553
static 553
Hemoarthrosis 625
Hemodialysis 674, 677
Hemodynamic monitoring 807
Hemoglobin 598
Hemolytic facies 610
Hemolytic uremic syndrome 664
atypical 665
typical 664
Hemophagocytic lymphohistiocytoses 651
diagnostic criteria 651
familial 651
infection-associated 651
secondary 652
Hemophilia 625
factor replacement therapy 626
fVIII or fIX antibodies (inhibitors) 626
Hemophilia C 627
Hemoptysis 442
Hemorrhages, subconjunctival 780
Hemorrhagic
disease of newborn 357
disorders 620
fevers 175
strokes 552
Hemostasis, physiology of 619
Hemothorax 475
Henderson-Hasselbalch equation 123
Henoch-Schönlein purpura 747
Hepatic encephalopathy 422
Hepatitis A vaccine 155
Hepatitis B vaccine 152
Hepatoblastoma 650
Hepatomegaly 417
causes 417
differential diagnosis 418
Hepatopulmonary syndrome 425
Hepatotropic viral infections 419
Hereditary
angioedema 136
elliptocytosis/stomatocytosis 608
nephropathies 660
spherocytosis 607
Herpangina 217
Herpes labialis 759
Herpes simplex 223
perinatal 223
Herpes zoster 213, 759
Hers disease 288
Hess test 620
Heterochromia iridum 782
HHV 6/7 illnesses 212
Hiatus hernia 389
Hiccups 442
Hiccups in newborn 314
Hidrotic ectodermal dysplasia 754
High frequency ventilation 801
High-risk newborn 314
High-risk pregnancies 294
Hind milk 69
Hirschberg's test 788
Hirschsprung's disease 392
Histiocytosis 650
History taking 850
developmental history 853
dietary history 853
environmental history 854
family history 852
general considerations 850
history of present illness 851
immunization history 853
Kuppuswami classification 854
past history 852
perinatal history 853
personal history 854
presenting complaints 851
socioeconomic history 854
system review 852
HIV infection in children
antiretroviral therapy 239
clinical staging 239
immunological staging 239
opportunistic infections 241
HIV-exposed infant 236
antiretroviral prophylaxis 236
cotrimoxazole prophylaxis 237
early infant diagnosis 238

infant feeding guidelines 236
immunization guidelines 237
Hives, *see* Urticaria
Hodgkin lymphoma 643
Holoprosencephaly 559
Holt-Oram syndrome 721
Home-based newborn care 836
Homocystinuria 282
Honeycomb appearance 466
Honeymoon period 715
Hookworm infestation 258
Hordeolum internum or externum 777
Horseshoe kidney 659
Herpes simplex infection 223
perinatal 353
Human milk banking 77
Human milk fortifiers 326
Human papillomavirus (HPV) vaccines 154
Humanized neonatal care 315
Humoral immunity 131
Hunter syndrome 289, 290
Hyaline membrane disease 332
diagnosis 333
management 333
pathogenesis 332
prevention 333
Hydatid cyst 259
Hydranencephaly 559
Hydrocarbon pneumonia 464
Hydrocele 688
transitory 313
Hydrocephalus 560
Hydrops fetalis 340
Hydrops, acute 413
Hydrothorax 474
Hyper IgM syndrome 137
Hyperaldosteronism 704
Hyperammonemia 284
Hypercalcemia 122
Hypercoagulable states 628
Hyperhemolytic crises 613
Hyperhidrosis 774
Hyper-IgE syndrome 136
Hyperinsulinemic states 717
Hyperkalemia 120
causes 119
treatment 120
Hyperleukocytosis 638
Hypermagnesemia 123
Hypermetropia 787
Hypernatremia 118
causes 118
treatment 119
Hyperparathyroidism 700
Hyperpituitarism 693
Hypersensitivity disorders 140
Hypersplenism 634
Hypertelorism 721
Hypertension
in children 523
diagnosis 524
management 525
persistent 524
severity 524
screening 524
transient 524
Hypertensive
crisis/encephalopathy 525
retinopathy 785
Hyperthermia 331
Hyperthyroidism 699
Hypertrichosis 773
Hypervitaminosis A 100
Hypervitaminosis D 109
Hypocalcemia 121
causes 121
management 121
Hypocalcemia in newborn 359
Hypochondroplasia 730
Hypoglycaemia
beyond neonatal period 716
in newborn 358
ketotic 717
reactive 717
Hypohidrosis 774
Hypokalemia 119
causes 119
treatment 119, 120
Hypokalemic periodic paralysis 594
Hypomagnesemia 122
causes 123
in newborn 359
treatment 122
Hypomelanosis of Ito 577
Hyponatremia 117
causes 118
treatment of 118
Hypoparathyroidism 699
Hypophosphatemia 108
Hypopituitarism 692
acquired 692
congenital 692
Hypospadias 682, 865
classification 682
Hyposplenic states 634
Hypotelorism 721
Hypothalamus-hypophyseal axis 691
Hypothermia in newborn 329
management 329
pathogenesis 329
prevention 329
Hypothyroidism 695
cause 695
clinical features 696
diagnosis 696
management 696
neonatal screening 696
types
congenital 695
juvenile 697
subclinical 697
Hypotonia, benign congenital 594
Hypotonic-hyporesponsive episodes 148
Hypoxic-ischemic encephalopathy 317
management 317
pathogenesis 317
severity grading 317

I

IAP growth reference norms 12
I-cell disease 287
Ichthyosis 755
Icterus, *see* jaundice
Idiopathic
hypercalciuria 664, 679
hypereosinophilic syndrome 618
intracranial hypertension 538
scoliosis 727
tibia vara 724
IgA nephropathy 664
IgA vasculitis, *see* Henoch-Schönlein purpura
Imerslund syndrome 103, 606
Immune reconstitution inflammatory syndrome 242
Immune thrombocytopenic purpura (ITP) 622
chronic ITP 623
maternal ITP and newborn 624
persistent ITP 623
Immunization 144
active immunization 144
adolescents 160
catch-up 160
determinants 145
in specific situations 160
pain and anxiety reduction 169
passive immunization 144
physiology 144
schedule, IAP 159
schedule, National 158
Immunogenicity 145
Immunoglobulins 133
Immunological defense mechanisms 134
Impetigo contagiosa 756
Inconsolable cry 148
Incontinentia pigmenti 577, 768
India Newborn Action Plan (INAP) 835
Indian childhood cirrhosis 427
Infant and young child feeding 80
Infant of diabetic mother 360
Infant feeding tube 884
Infant milk Substitutes, Feeding Bottles and Infants Food Act, 1992 78
Infant mortality rate 2, 830
Infantile
hemangioma 754
colic 57
hypertrophic pyloric stenosis 389
Refsum disease 285
spasms 548
tremor syndrome 556
Infantometer 13, 886
Infections in diabetics 715
Infectious mononucleosis 224
Infective endocarditis 515
antimicrobial prophylaxis 516
clinical presentation 515
diagnosis 515
treatment 515
Inflammatory bowel diseases 406
Influenza 228
antiviral therapy 229
categorization, diagnosis and management 229
epidemiology 228
influenza-like illness 228
prevention 229
Influenza vaccines 156
Infranuclear facial palsy 529

In-grown nails 775
Inguinal hernia 395
Injectable polio vaccine (IPV) 149
Injections
  intradermal 868
  intramuscular 868
  subcutaneous 868
Innate immunity 131
Inspissated bile syndrome 345
Insulin preparations 713
Insulin shock 715
Integrated child development services 833
Integrated management of neonatal and childhood illnesses 842
  color-coded triage system 842
  general process 842
  classification, for
    anemia (6 mo–2 yrs) 846
    ear problems (2 mo–5 yrs) 846
    cough/difficult breathing (2 mo–5 yrs) 844
    diarrhea (2 mo–5 yrs) 845
    diarrhea in young infants (up to 2 mo) 848
    feeding problems (up to 2 mo) 848
    fever (2 mo–5 yrs) 845
    jaundice in young infant (up to 2 mo) 848
    malnutrition (2 months–5 years) 846
    possible serious bacterial infection (up to 2 mo) 847
Intellectual disability 43
  severity grading 44
Interstitial lung diseases 469
In-toe/out-toe walking 728
Intra/periventricular haemorrhage 318
  pathogenesis 318
  USG criteria for severity of IVH 318
Intracranial space-occupying lesions 574
Intra-hepatic biliary atresia 345
Intraosseous cannulation 807
Intrauterine growth retardation 326
  categories
    asymmetrical 327
    symmetrical 327
  causes 327
  complications 327
  mixed 327
Intrauterine infections 349
  clinical indicators 350
  diagnosis 350
Intrauterine pneumonia 335
Intravenous immunoglobulins 170
Intussusception 410
Iodine deficiency disorders 698
Iridocyclitis 781
Irritable bowel syndrome 378
Isovaleric academia 284
Intravenous transfusion set 872
Ivy bleeding time 621

J

Janani Shishu Suraksha Karyakaram 835
Janeway lesions 515
Janz syndrome, *see* Juvenile myoclonic epilepsy
Japanese encephalitis vaccine 154
Jatene arterial switch operation 505
Jaundice
  post-neonatal causes 418
  post-neonatal diagnostic evaluation 418
  post-neonatal differential diagnosis 419
Jaw jerk 529
Jaw-thrust maneuver 792
Jejunoileal atresia 391
Jitteriness 354
Jugular venous pressure 482
Juncs food, IAP guidelines 37
Juvenile delinquency 840
Juvenile Justice Act, 2015 841
Juvenile myoclonic epilepsy 548

K

Kahn's recovery syndrome 95
Kala-azar 252
Kangaroo mother care 311, 325, 330
  benefits 330
  monitoring 331
  prerequisites 330
  procedure 330
  when to stop 331
Kasabach-Merritt syndrome 624, 755
Kawasaki disease 748
  diagnostic criteria 749
  echocardiography 749
  treatment 749
Kayser-Fleischer ring 427
Keloids 772
Keratitis/corneal ulcer 780
Keratoconus 780
Kernicterus 343
Kernig sign 528, 565
Ketogenic diet 550
Kindling 541
Kleihauer-Betke test 358
Klinefelter syndrome 274
  clinical spectrum 274
  cytogenetics 274
  diagnosis 274
Klippel-Feil anomaly 725
Klippel-Trenaunay-Weber syndrome 754
Klumpke's paralysis 320
Knock knee, physiological 723
Kocher Debre semelaigne syndrome 594, 697
Koebner response 768
Krabbe disease 287, 582
Kussmaul breathing 125, 433
Kwashiorkor 87
Kyasanur forest disease 223

L

Lacrimal mucocele 778
Lactation
  anatomy 70
  counseling 75
  physiology 70
  ten steps 76
Lactational failure 74
Lactic acidosis 289
Lacunar skull 720
Lagophthalmos 777
Landau-Kleffner syndrome 549
Langerhans cell histiocytosis 650
Langerhans cells 650
Lanugo 306
Large for date babies 327
Laron syndrome 38
Larva migrans, *see* Toxocariasis
Laryngeal mask airway 796
Laryngitis, acute infectious 450
Laryngitis, acute spasmodic 450
Laryngomalacia 336, 451
Laryngoscope 875
Laryngotracheobronchitis, acute 449
Late metabolic acidosis 360
Late neonatal mortality rate 293
Lazy leukocyte syndrome 136
Lead-pipe rigidity 530
Learning disorders or disabilities 45
  early indicators 46
Legg-Calve-Perthes disease 735
Leg-length discrepancy 728
Leishmanin test 253
Length/height 13
Lennox-Gastaut syndrome 548
Lentigines 761
Leprosy 201
Leptospirosis 242
  clinical spectrum 242
  diagnosis 242
  treatment 243
Letterer-Siwe disease 650
Leucorrhoea, physiological 367
Leukemoid reactions 616
Leukocoria 648, 782
Leukodystrophy, metachromatic 581
Leukonychia 775
Leukopoiesis 598
Lichen nitidus 769
Lichen planus 769
Lid coloboma 777
Limb girdle muscular dystrophy 593
Limping child 728
Linear nevus syndrome 577
Lipid storage disorders 286
Lipodystrophy 772
Lipoid pneumonia 465
Liquid ventilation 801
Lisch nodules 782
Lissencephaly 560
Listeriosis 348
Liver
  abscess 423
  biopsy 417
  function tests 416
  injury, drug-induced 200
Loeffler syndrome 465
Long QT syndrome 521
Lorber's criteria 559
Low birth weight rate 293
Low-vision 787
Ludwig angina 207
Lumbar puncture 879
Lung abscess 467
Lung scintigraphy 438
Lung surfactant 430
Lupus cell 739
Lyme disease 742
Lymphadenopathy 635, 859
Lymphadenopathy, physiological 635
Lymphadenopathy, tubercular 635
Lymphangitis 636
Lymphedema 636

Lymphocytopenia 619
Lymphocytosis 619

M

Macewan sign 561, 861
Macroglossia 385
Macrophage activation syndrome 741
Magnesium 122
  physiology 122
  recommended dietary allowance 122
  sources 122
Major histocompatibility complex 131
Malabsorption syndromes, *see* chronic diarrhea
Malaria
  chronic malaria 247
  diagnosis 248
  epidemiology 245
  life-cycle 246
  malaria vaccines 251
  management 249
  neonatal malaria 247
  optimal test 248
  parasight-F test 248
  parasite index 248
  rapid diagnostic tests 248
  severe malaria, WHO criteria 247
  thick and thin smear 248
  treatment failure 251
  treatment
    of uncomplicated malaria 250
    of severe malaria 250
  vaccine 157
Male pseudohermaphroditism 707
Malecot's catheter 885
Malrotation 392
Mantoux test, *see* tuberculin sensitivity test
Maple syrup urine disease 283
Marasmus 87
Marble-bone disease, *see* Osteopetrosis
Marfan syndrome 40
Maroteaux-Lamy syndrome 290
Marshal and Tanner staging 709
Mastitis neonatorum 313
Mastoiditis 449
Masturbation 62, 368
Maternal mortality rate 293
McArdle disease 288
McBurney's point 411
McCune Albright syndrome 761
M-Chat 51
Measles 209
  clinical manifestations 209
  complications of 210
  outbreak-control 210
  pathogenesis 209
  prevention 210
Measles containing vaccines 151
Measles-rubella (MR) elimination 210
Meatal stenosis 689
Mechanical ventilation
  controlled 800
  indications 800
  spontaneous 801
  synchronized 801
Meckel's diverticulum 392
Meckel's scan 392
Meconium 313
Meconium aspiration syndrome 334
Meconium ileus 468
Median value 11
Medium chain acyl-CoA dehydrogenase deficiency 285
Medulloblastoma 577
Megalencephaly 562
Megalocornea 780
Melanocytic nevi 761
Membranous nephropathy 664
Menghini's aspiration needle 881
Meningitis, aseptic (Lincoln's) 568
Meningitis, bacterial 565
  antimicrobial therapy in 567
Meningitis, recurrent 565
Meningitis, tubercular 567
Meningococcal infections 187
  clinical spectrum 187
  prevention 188
Meningococcal vaccines 156
Meningococcemia 187
Meningomyelocele 558
Menkes (kinky hair) disease 582
Menkes-kinky-hair syndrome 112, 773
Mesial temporal sclerosis 549
Mesomelia 729
Metabolic acidosis 125
  causes 125
  management 126
Metabolic alkalosis 126
  causes 126
  management 126
Metabolic monitoring 807
Metachromatic leukodystrophy 287
Metatarsus adductus or varus, congenital 725
Metered dose inhaler 876
Methemoglobinemia 609
Methylmalonic aciduria 284
Microcephaly 560, 720
Microcornea 780
Microdeletion syndrome 272
Microdeletions 266
Microdrip set 872
Micrognathia/retrognathia 721
Micropenis 689, 708
Mid-day meal program 98
Middle lobe syndrome 471
Mid-upper arm circumference 8, 13
Migraine 540
Mikulicz syndrome 778
Milia 311
Miliaria 774
Miliaria crystalline 763
Miliaria rubra 762
Milk-alkali syndrome 122
Milk-aspiration syndrome 464
Miller-Fisher syndrome 588
Milroy disease 312
Minimum dietary diversity 79
Minimum meal frequency 79
Missed (catch-up) immunization 159
Mission Indradhanush 163
Mitochondrial disorders 268
Mitral regurgitation 511
Mitral stenosis 512
Mitral valve prolapse 512
Mittendorf 's dots 776, 784
Mixed connective tissue disease 747
Mixed hemoglobinopathies 612
MMR vaccine 151
Mobitz type II 521
Moderate acute malnutrition, diagnostic criteria 91
Modified ballard scoring system 323
Modified Glasgow coma scale 535
Modified measles 210
Modified Ross classification 492
Modified varicella-like illness 212
Molluscum contagiosum 759
Molybdenum deficiency 112
Mongolian spots 312, 761
Mongoloid slant 778
Morbidity indicators 1
Morbilliform drug eruptions 763
Morquio syndrome 290
Mortality indicators 1, 2
Mosaicism 269
Mosteller's formula 888
Mother to child protection card 15
Mother-neonatal intensive care unit 315
Movement disorders 554
Movement disorders, stereotypic 556
Movement therapy, constraint-induced 564
Moyamoya disease 551
Moyamoya syndrome 551
MR vaccine 151
Mucopolysaccharides 289
  classification 289
Multicystic dysplastic kidney 659
Multifactorial disorders 268
  recurrence risk 268
Multi-organ dysfunction syndrome 804
Multiple malformation syndrome 361
Multiple pregnancy 297
  complications 298
  dizygotic 298
  monozygotic 298
  siamese twins 298
Multiple sclerosis 582
Multisystem inflammatory syndrome in children (MIS-C) 227
  investigation 227
  management 227
  WHO diagnostic criteria 227
Mumps 213
  clinical manifestations 214
  complications 214
  mump's embryopathy 214
  prevention 214
Munchausen by proxy syndrome 64
Murine typhus 208
Murmur, functional 485
Murmur, grades 485
Muscle power 530
Musculoskeletal trauma 813
Mutation 265
Myasthenia gravis 590
  myasthenic syndromes, congenital 591
Mycoplasma infections 245
Myelodysplastic syndrome 616
Myocarditis 516
Myoclonic seizures 548
Myopathies, congenital 594
Myopathies, mitochondrial 594
Myopia 788
Myotonic muscular dystrophy 593

N

Nadas' criteria 507
Nail-biting 60
Nail-patella syndrome 679, 775
Narcolepsy 62, 551
Nasal cannula 873
Nasal catheter 874
Nasogastric intubation 884
Nasogastric tube 884
Nasolacrimal duct obstruction 778
Nasopharyngeal airway 796
Natal tooth 313
National Control of Diarrheal Diseases Programme 401
National Control Programme Against Nutritional Blindness 100
National Framework of Malaria Elimination 252
National Guidelines for clinical management of dengue fever 219
National Health Mission 832
National Health Policy, targets 830
National Health Policy 4, 829
National health programs 832
National Immunization Day 216
National Institute of Mental Health and Neurosciences index 46
National Iodine Deficiency Disorders Control Programme 698
National Iron Plus Initiative Programme 605
National Kala-azar Elimination Programme 253
National Leprosy Eradication Programme 203
National Nutrition Policy 98
National Rural Health Mission 832
National Tuberculosis Elimination Programme 201
National Urban Health Mission 832
National Vector Borne Disease Control Programme 836
National Vector Borne Diseases Control Programme (Malaria) 251
Natural immunity 144
Navjaat Shishu Suraksha Karyakram 835
Nebulizer 878
Needle, lumber puncture 879
Needle, scalp vein (butterfly) 869
Needle, tru-cut 881
Needle, Vim Silverman 881
  with Franklin modification 882
Neonatal adrenoleukodystrophy 285
Neonatal apnea 336
Neonatal cholestasis 344
  disorders 344
  management 344
Neonatal conjunctivitis 778
Neonatal Graves' disease 699
Neonatal hepatitis 344
Neonatal intensive care units 315
Neonatal jaundice 337
  age of onset 339
  causes 338
  diagnostic approach 338
Neonatal lupus 745
Neonatal mortality rate 2, 293
Neonatal necrotizing enterocolitis 348
  staging, Bell's criteria 349
Neonatal purpura 624
Neonatal reflexes 308
  asymmetrical tonic neck reflex 310
  aymmetric tonic neck reflex 310
  crossed-extension reflex 310
  Landau reflex 310
  Moro's reflex 310
  palmar grasp reflex 310
  parachute reflex 310
  plantar grasp reflex 310
  prechtl stages 308
  startle reflex 310
  stepping reflex 310
  sucking reflex 310
  walking reflex 310
Neonatal resuscitation 299
Neonatal resuscitation program 301
  chest compressions 303
  corrective steps 303
  endotracheal (ET) intubation 303
  golden minute 301
  initial assessment 301
  initial steps 301
  medications 304
  neonatal resuscitation algorithm 302
  positive pressure ventilation 301
Neonatal seizures 354
  causes 354
  clinical types 354
  diagnostic approach 354
  management 355
Neonatal septicemia 347
  clinical presentation 347
  diagnosis 347
  management 348
  microbial etiology 347
  risk factors 347
  sepsis screen 347
Neonatal sleep myoclonus, benign 551
Neonatal stridor 336
Neostigmine response test 590
Nephrolithiasis 685
  prevention 685
  predisposing factors 685
Nephrotic syndrome 666
  causes 666
  complications 668
  congenital 671
  course 668
  Finnish-type 671
  histological types 666
  Management
    of first attack 669
    algorithm 669
    of subsequent relapses 670
    of frequent-relapsers or steroid-dependent cases 670
  pathogenesis 667
  secondary 671
  treatment of steroid-resistant cases 670
Nervous system, examination of 528
Neural tube defects 557
  folic acid supplements 559
  prevention 559
  segmentation defects 559
Neuroblastoma 646
  INSS staging system 646
Neurocysticercosis 574
Neurodegenerative disorders 580
Neurofibromatosis (NF) 577
Neurohormones of hypothalamus 691
Neuroimaging studies 533
Neurological monitoring 807
Neuromuscular disorders 586
Neuronal ceroid lipofuscinoses 582
Neuronal migration defects 560
Neuropathic bladder 684
Neutropenia 617
Neutrophilia 618
Newborn care corner 315
Newborn stabilization units 315
Next generation sequencing 276
Niacin (B3) deficiency 102
Niemann-Pick disease 286
Night blindness 99
Night-terrors 62
Nikolsky sign 766
Nipple discharge in adolescents 366
Nipples, flat or inverted 73
Nipples, sore 73
Nipples, syringe (Kesri) method 73
Nitric oxide ventilation 801
Noisy breathing in newborn 314
Noma neonatorum (cancrum oris) 207
Noma neonatorum 347
Non-alcoholic fatty liver disease 427
Non-Hodgkin's lymphoma 644
  St. Jude staging system 645
Non-invasive prenatal screening 272
Non-ketotic hyperosmolar coma 712
Non-nutritional rickets, indicators 108
Non-nutritive sucking 74, 97, 326
Non-typhoidal salmonellosis 185
Noonan syndrome 274
Normal newborn care 310
  levels of care 315
  of eyes 311
  of skin 311
  of umbilical stump 311
Nosocomial infections 260
  high-risk factors 260
  outbreak control 261
  prevention 261
Nuchal rigidity 528, 565
Nummular eczema 770
Nursemaid elbow 725
Nurturing care 18
Nutrition in critically sick child 808
Nutritional assessment 84
Nyctalopia 787
Nystagmus 789

O

Obesity 34
  endogenous (secondary) obesity 35
  exogenous (constitutional) obesity 35
  extreme obesity 35
  monogenic obesity 35
  overweight 34
  polygenic obesity 35
Obstructive sleep apnea disorders 447
Obstructive uropathy 683
Ocular bobbing 789
Ocular dysmetria 789
Ocular injuries 785

Omphalitis, *see* Umbilical sepsis
Omphalocele 307, 395
Oncological emergencies 639
Onion-peel appearance 649
Open-vial policy 167
Ophthalmia neonatorum 346
Ophthalmitis, sympathetic 782
Oppenheim's maneuver 530
Opportunistic infections 137
  diagnostic evaluation 139
  predisposing factors 138
Opsoclonus 789
Opsoclonus-myoclonus 646
Optic atrophy 785
Optic nerve glioma 785
Optic neuritis 785
Oral iron therapy 604
Oral polio vaccine (OPV) 149
Oral rehydration therapy 398
Organic academia 283
Orifice counting 299
Oro-facial digital syndrome 721
Oropharyngeal airway 796, 873
ORT corners 401
Ortolani test 722
Osgood-Schlatter's disease 735
Osler nodes 515
Osmolality, plasma 114
Osmotic fragility test 607
Osteochondritis dissecans 735
Osteochondroma 736
Osteochondroses 734
Osteodysplasias 729
Osteogenesis imperfect 730
Osteoid osteoma 736
Osteomyelitis 731
Osteopetrosis 731
Osteosarcoma 648
Otalgia 448
Otitis externa 448
Otitis media 448
  recurrent 449
  risk factors 448
Ovarian hormones 706
Over the needle catheters 869
Oxygen delivery devices 873
Oxygen hood/tents 874
Oxygen therapy 796
Oxytocin reflex 71
Ozen criteria 750

P

Pallor 859, also *see* anemia
Palpitation 481
Pancreatitis, acute 412
Pancreatitis, chronic or recurrent 412
Pancreatitis, juvenile tropical 412
Panner's disease 735
Panniculitis 772
Panophthalmitis 781
Papilledema 785
Paradoxical breathing 434
Parainfluenza viral infections 229
Paraneoplastic syndromes 646
Paraphimosis 689
Paraplegia 584
  diagnostic approach 585
  flaccid 585
  in extension 585
  in flexion 585
  spastic 585
Parapneumonic effusions 473
Parasomnia 62
Parathyroid disorders 699
Parenteral iron therapy 604
Parenteral fluid therapy 127
  fluid requirements in normal children 128
  fluid therapy in critically sick children 129
  fluid therapy in diarrhea 129
  fluid therapy in gastric losses 129
  fluid therapy in malignancy 130
  fluid therapy in surgery 130
  hypernatremic dehydration 129
  hyponatremic dehydration 129
  isonatremic dehydration 128
  principles of 128
Paronychia, acute 775
Paronychia, chronic 775
Parotitis 385
Paroxysmal nocturnal hemoglobinuria 608
Paroxysmal non-epileptic events 550
Paroxysmal vertigo, benign 550
Parvoviral illnesses 211
Passive immunization 170
Patau syndrome 272
Patent ductus arteriosus (PDA) 497
  course and complications 498
  hemodynamics 498
  management 499
  medical closure 499
  signs 498
Peak expiratory flow meter 879
Peak expiratory flow rate 454
Peak flowmetry 437
Pectus carinatum 727
Pectus excavatum 727
Pediatric advanced life support 790, 795
Pediatric airway 795
Pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus pyogenes* (PANDAS) 179
Pediatric chain of survival 795
Pediatric intensive care unit
  admission criteria 806
  consensus guidelines 806
Pediatric trauma score 811
Pediculosis 759
Pedigree charting 275
Pelkan spur 105
Pellagra 102
Pelvi-ureteric junction (PUJ) anomalies 681
Pemphigus vulgaris 767
Penetrance 265
Percentiles 11
Perianal abscesses 411
Pericardiocentesis 523, 883
Pericarditis 522
  causes of 522
  clinical manifestations 522
  constrictive 522
  diagnosis 523
  management 523
Perinatal HIV infection 233
  clinical presentation 233
  diagnosis in children
    >18 months 235
    <18 months 235
  pathogenesis 233
  prevention of infection 235
  risk factors 233
  universal safety precautions 236
Perinatal mortality
  causes 293
  rate 2, 292
Perinatal pneumonia 335
Periodic breathing 336
Peripheral neuropathies 588
Peripheral neuropathy, post-diphtheritic 589
Peripheral smear 599, 601
Peripheral venous cannulation 806, 870
Peritoneal dialysis 674
peritoneal dialysis, continuous 677
Peritonitis, acute 413
Peritonitis, tubercular 414
Peroneal muscular atrophy 589
Persistent hyperplastic primary vitreous 784
Persistent pulmonary hypertension in newborn 336
Pes cavus 725
Pes planus 725
Peutz-Jeghers syndrome 392
Phagocytic disorders 135
Phagocytic system 132
Phenotype 265
Phenylketonuria 281
Pheochromocytoma 705
Philadelphia chromosome 643
Phimosis 689
Phimosis, physiological 313
Phlycten 779
Phlyctenular keratoconjunctivitis 779
Phocomelia 721
Phosphoryl kinase deficiency 288
Photoallergic reaction 765
Photophobia, physiological 313
Photosensitivity rash 764
Phototherapy 341
Phototoxic reaction 765
Physical activity, WHO guidelines 37
Physiological jaundice 312, 337
  cardinal features 337
  clinical assessment, Cramer criteria 338
  etiophysiology 337
Physiology of
  adrenal functions 700
  digestion 373
  liver functions 416
  lymphatic system 634
  parathyroid functions 699
  puberty 708
  renal functions 654
  respiration 432
  sex differentiation 706
  sex steroids 705
  thyroid functions 695
Pica 58
Pickwickian syndrome 35
Picky-eating 57
Pierre Robin syndrome 383, 721
Pigeon chest, *see* Pectus carinatum
Pigmentation, corneal 781

Pili torti 773
Pincer grasp 23
Pinguecula 780
Pinworm, *see* Enterobiasis 257
Pituitary disorders 691
Pituitary hormones 692
Pityriasis alba 762
Pityriasis rosea 769
Placental examination 300
Plagiocephaly 720
Platelet disorders 622
Platelet function defects 624
Platelet function tests 621
Pleural effusion 474
Pleural effusion in newborns 336
Pleurisy, dry to plastic 474
Pleurodynia 218
Pneumatoceles 461
Pneumococcal conjugate vaccine 153
Pneumococcal infections 180
  clinical spectrum 180
  prevention 180
Pneumococcal polysaccharide vaccine 154
Pneumomediastinum 476
Pneumonia 460
  atypical or bacterial 463
    Mycoplasma 463
    Chlamydia 463
    Legionnaire's 463
  community-acquired 460
  H. influenzae B 461
  non-infective
    hydrocarbon pneumonia 464
    aspiration pneumonia 464
    milk-aspiration syndrome 464
  nosocomial 460
  pneumococcal 461
  recurrent, risk factors 460
  staphylococcal 461
  viral 461
  antimicrobial therapy in 463
Pneumonia, primary atypical 245
Pneumothorax 475
Pneumothorax in newborns 336
Poisoning in children 820
  antidotes 822
  preventive measures 823
  principles of management 820
  risk factors 820
  specific poisoning
    barbiturate poisoning 825
    corrosive poisoning 823
    dhatura (belladonna) poisoning 824
    hydrocarbon (kerosene) poisoning 823
    iron poisoning 826
    lead poisoning 827
    naphthalene poisoning 825
    opioids (narcotics) poisoning 824
    organophosphorus (op) poisoning 824
    paracetamol poisoning 826
    phenothiazine poisoning 825
    salicylate poisoning 827
Poland syndrome 593
Polio Eradication in India 215
Poliomyelitis 214
Polyarteritis nodosa 749
Polycystic kidney disease 660
Polycythemia 616
  in newborn 358
Polydactyly 721
Polysplenia or accessory spleen 634
Pompe disease 288
Ponseti method 724
Popliteal (Baker) cyst 736
Porencephaly 559
Porphyria 290
  cutanea tarda 291
Portacaval shunts 429
Portal hypertension 428
    causes 428
    clinical features 428
    management 429
Port-wine stains 754
Poshan abhiyaan 98
Possetting 377
Posterior urethral valves 681
Post-maturity 328
Postnatal
  aspiration pneumonia 335
  circulation 479
  pneumonia 335
Post-traumatic stress disorder 64
Potassium 119
  physiology 119
Pott's spine 733
Prader-Willi syndrome 272
Pre-lacteal feeds 71
Prematurity 321
  causes 321
  clinical attributes 322
  complications 324
  physiological handicaps 323
Prenatal diagnosis 279
Preterm child
  fluids requirement 325
  management 324
  micronutrient supplementation 325
  modes of feeding 326
  nutritional requirements 325
Prickly heat 762
PRINTO classification 739
Prism scoring 809
Prognathia 721
Prolactin reflex 71
Propionic aciduria 284
Proptosis 776
Protection of Children from Sexual Offenses Act (POCSO), 2012 838
Protective efficacy 145
Proteins 67
Proteinuria 666
  causes of 666
Proteinuria, orthostatic 666
Proteinuria, tubular 666
Proteus syndrome 593
Prothrombin time 621
Prune-Belly syndrome 681
Pseudocyst of pancreas 412
Pseudo-Hurler polydystrophy 287
Pseudohypertrophy 592
Pseudohypoparathyroidism 700
Pseudomembranous colitis 206
Pseudoseizures, *see* Paroxysmal non-epileptic events
Pseudotumor cerebri, *see* Idiopathic intracranial hypertension
Pseudoxanthoma elasticum 756
Psoriasis 768
Pterygium 780
Ptosis 777
Pubertal changes in adolescents 363
Puberty, delayed 710
  hormonal therapy in 710
Puberty, precocious 709
  central 709
  peripheral 709
  incomplete 709
Puddle sign 374
Puhl's lesion 191
Pulmonary arterial hypertension 487
Pulmonary function test 436, 469
Pulmonary oligemia 487
Pulmonary stenosis 501
Pulmonary venous hypertension 487
Pulse 481, 858
Pulse polio immunization 216
Pulseless electric activity 799
Purpura fulminans 629
Pustular melanosis 312
Pyoderma, *see* Impetigo contagiosa
Pyrexia of unknown origin 174
  causes 175
  laboratory investigations 175
Pyruvate kinase deficiency 609

Q

Q fever 208
Quinsy, *see* Peritonsillar abscess

R

Rabbit nose 443
Rabies 230
  clinical manifestations 230
  pathogenesis 230
  prevention 231
Radial club hand 721
Rag-doll appearance 595
Rail-road or tram-track appearance 580
Raised intracranial pressure 537
  causes 538
  clinical presentation 537
  management 538
  pathophysiology 537
Ramstedt's pyloromyotomy 390
Ranula 385
Rashes in newborn 312
Rashtriya Bal Swasthya Karyakram 834
Rashtriya Kishor Swasthya Karyakram 836
Raynoud phenomena 746
Red blood cell indices 600
RCH portal 833
Reactive lymphadenitis 635
Ready-to-use therapeutic food 96
Recommended dietary allowances 66
Recovery position 791
Rectal prolapse 411
Recurrent apnea in newborn 337
Recurrent respiratory infections 439
Red-eye 779
Reed-Sternberg cell 643
Re-feeding (recovery) syndromes 95
Reference curves 15
Reflex or automatic bladder 531

Refractive errors 787
Re-lactation 74
drip and drop method 74
Renal
agenesis 659
biopsy 658
calculi, *see* Nephrolithiasis
function tests 657
immaturities in newborn 655
malformations 658
monitoring 807
replacement therapy 676
scan 657
transplantation 677
tubular acidosis 677
vein thrombosis 665
Reproductive, maternal, newborn, child and adolescent health (RMNCH+A) approach 833
Rescue breathing 792
Respiratory
acidosis 126
causes 127
management 127
alkalosis 127
distress in children, causes 440
distress in newborn 331
causes 331
diagnostic approach 331
distress score 331
monitoring 807
Respiratory syncytial virus 230
Resuscitation bag 797
Reticulocyte count 601
Retinal detachment 784
Retinal hemorrhage/infarcts 784
Retinal phakoma 784
Retinitis pigmentosa 784
Retinoblastoma 648
Retinopathy of prematurity 783
classification 783
Retropharyngeal abscess 446
Rett syndrome 582
Revised Jones criteria (2015) 509
Reye syndrome 572
clinical staging 572
Rhabdomyosarcoma 649
Rhesus hemolytic disease of newborn 339
diagnosis 340
management 340
pathogenesis 339
prevention 340
Rheumatic (Sydenham)
chorea 509
carditis 509
disorders 738
clinical indicators of 738
clinical spectrum 738
laboratory diagnosis 738
management 739
fever 508
diagnosis, *see* Revised Jones criteria (2015)
etiopathogenesis 508
management 510
prevention 510
secondary prevention 510
heart disease 511
diagnostic approach 514
Rheumatoid factor 738
Rheumatoid nodules 740
Rhinitis, allergic 443
classification 444
management 444
mannerisms 443
step-wise management 444
Rhinovirus infections 229
Rhizomelia 729
Riboflavin (B2) deficiency 102
Rich's focus 191
Rickets
clinical manifestations: 107
clinical signs 107
etiological classification 106
IAP guidelines 2021 108
pathophysiology 106
prevention 108
radiological changes 107
stoss regimen 108
treatment 108
vitamin D deficiency 106
Rickettsial fevers 208
diagnosis 208
epidemiology 208
eschar formation 208
treatment 209
when to suspect 208
Riley-Day syndrome 595
Ringworm, *see* Dermatophytoses
Roach scale 580
Robertsonian translocation 266
Robin malformation sequence 361
Rochester criteria 173
Rocker-bottom foot 725
Rooming in 72, 310
Rose spots 184
Roseola infantum 211
Rotavirus vaccine 153
Roth spots 515, 784
Rothera's test 656
Round worm, *see* Ascariasis
Rubella (German measles) 210
Rubinstein-Taybi syndrome 272, 721
Rumination 58
Ryles tube 884

S

Sabin vaccine *see* Oral polio vaccine
Safe immunization practices 167
Salk vaccine *see* injectable polio vaccine
Salmon patch 754
Salmon patch, *see* Stork-bites 312
Salt and sugar solution 400
Salter and Harris classification 737
Sandhoff disease 582
Sanfilippo syndrome 290
Sarcoma botryoides 650
Sarnat and Sarnat classification 317
Scabies 759
Scaphocephaly 720
Scarlet fever 179
Schamroth sign 483
Scheie syndrome 290
Scheuermann's disease 735
Schilling test 104, 606
Schistosomiasis 259
Schizencephaly 560
Scholastic backwardness 49
Scholastic difficulties early warning signs 50
School health service 837
Scissoring 563
Scleredema adultorum 772
Sclerema neonatorum 772
Sclerocornea 781
Scleroderma 746
Sclerosing panencephalitis, subacute 581
Scorpion sting 818
Screen time, IAP guidelines 37
Scrotal swellings/masses 689
Scrub typhus 208
Scurvy 104
clinical manifestations 104
radiological finding 105
treatment 105
Sedation and analgesia 808
Seizure 540
causes 541
diagnostic evaluation 542
ILAE 2017 classification 541
management 543
Seizure disorders 540
Seizure mimics 550
Selective IgA deficiency 137
Selenium 112
deficiency 112
excess 112
Self-limited epilepsy with centrotemporal spikes 549
Sellick maneuver 797
Sengstaken-Blackmore tube 429
Sequestration crises 613
Sequestration, pulmonary 471
Seroconversion 145
Seroprotection 145
Serotype replacement disease 154
Sever disease 735
Severe acute malnutrition
antibiotic therapy 93
community based care 95
criteria for discharge 95
diagnostic criteria 91
facility-based care 91
in infants < 6 months 96
micronutrient supplements 94
ten steps of management 92
Severe combined immunodeficiency disorders 137
Severe feeding disorders 58
Sex chromosomal DSD 706
Sexual maturity 364
Sexually transmitted diseases 367
Shagreen patch 579
Shake test 333
Shakir's tape 85
Sheehan's focus 191
Shifting dullness 374
Shigellosis 185
complication 186
management 186
pathogenesis 186
Shock 802
causes 802
clinical signs 803
management 803
of septic shock 805
pathogenesis 803
pathophysiology 802

Short bowel syndrome 409
Short stature 37
  constitutional 38
  familial 38
  normal variant 38
  primary 38
  primordial 38
  secondary 38
Shoulder sign 390
Shuddering attacks 551
Shwachman-Diamond syndrome 408
Sick sinus syndrome 522
Sickle cell disease 612
Sickling test 613
Sillence classification 730
Simond's focus 191
Simple rubber catheter 884
Single umbilical artery 307
Sinus arrhythmia 519
Sinus bradycardia 519
Sinusitis 445
Sjogren syndrome 746
Skeletal dysplasia 728, 729
Skin-fold thickness 9
Skull fractures in newborns 320
Slipped capital femoral epiphysis 735
Sly syndrome 290
Smoke injury 465
Snake bite 817
Sneezing in newborn 314
Somatic cell disorders 269
Somatotypes (body build) 9
Somogyi phenomenon 715
Sore nipples 73
Sore throat, *see* Acute tonsillopharyngitis
Soto's syndrome 41
Soto's syndrome, *see* Cerebral gigantism
Spacers 877
Special newborn care unit 315
Spermatic cord, testicular torsion of 690
Spina bifida occulta 558
Spina ventosa 734
Spinal cord injuries 583
Spinal deformities 727
Spinal muscular atrophy 587
Splenectomy 634
Splenic injuries 634
Splenomegaly 632
  tropical 633
Splenosis 634
Splinter 515
Spondyloepiphyseal dysplasia 730
Spontaneous bacterial peritonitis 668
Sprengel deformity 725
Squint, *see* Strabismus
Stadiometer 13
Staphylococcal infections 178
  clinical spectrum 178
Staphylococcal scalded skin syndrome 758, 766
Stature, length or height 8
Status
  asthmaticus 454
  dystonicus 555
  epilepticus 542, 545
Steeple sign 449, 450
Stem-stature index 9
Sternocleidomastoid tumor 320
Steven-Johnson syndrome 766
Still's murmur 485
Stillbirth rate 292
Stokes-Adams syndrome 522
Stomatitis 384
Stool examination 374
Stork-bites 312
Stork-bites, *see* Salmon patch
Stork-neck deformity 589
Strabismus 788
  non-paralytic 788
  paralytic 788
Stranes procedure 506
Stranger anxiety 64
Straw berry tongue 748
Street children 839
Streptococcal infections 179
  clinical spectrum 179
Streptococcal sore throat 446
Striae cutis distensae 772
Stridor 440
  causes 441
String sign 390
Strongyloidosis 258
Sturge-Weber syndrome 580, 754
Stuttering or stammering 61
Stye 777
Subacute combined degeneration of cord 103
Subacute sclerosing panencephalitis 210
Subcutaneous fat necrosis 313, 772
Subcutaneous nodules 509
Substance abuse 368
Sucking pads/sucking callus 313
Sudamina rash 763
Sudden infant death syndrome 827
Sulfosalicylic acid test 656
Sunburn, acute 764
Sun-ray or sun-burst appearance 649
Sunset sign 562
Superficial reflexes 530
Superior vena caval syndrome 638
Supplementary sucking techniques 97
Supra-pubic puncture 883
Supraventricular tachycardia 520
Surfactant replacement therapy 334
Sustainable development goals 829
Sweat chloride test 468
Swyer-James syndrome 452
Symblepharon 780
Symptomatic seizures 541
Syncope 550
Syndactyly 721
Syndrome of inappropriate ADH 691
Syringe (Kesri) method 73
Syringe, autodisabled 867
Syringe, tuberculin or insulin 868
Syringomyelia 584
Systemic lupus erythematosus 743
  EULAR/ACR criteria 744

T

T lymphocytes 133
Talipes calcaneovalgus 725
Talipes equinovarus, congenital 724
Tall stature 40
Tandem walking 530
Tanner's sexual maturity rating 364
Tap
  dry 881
  subdural 880
  ventricular 880
Tapeworm, intestinal 258
Target (bulls-eye) lesions 767
Target (doughnut) sign 390
Tarui disease 288
Tay-Sach disease 582
TB preventive therapy (TPT) 200
T-cell disorders 137
Td vaccine 149
Tdap vaccine 149
Teen pregnancy 369
Teen-suicide 369
Temper tantrum 63
Testicular appendix, torsion of 690
Testicular hormones 705
Tetanus 203
  clinical stages 204
  complications 204
  modified patel and jog criteria 205
  neonatorum 203
  pathogenesis 203
  post-injury immunization for TT 206
  prevention 205
  treatment 204
Tetany 121
  chvostek sign 121
  Erb's sign 121
  latent tetany 121
  peroneal sign 121
  treatment 122
  Trousseau sign 121
Tethered cord syndrome 584
Tetralogy of Fallot 503
  hemodynamics 503
  signs 504
Thalassemia 609
  α 612
  intermedia 609
  major 609
  minor 609
  secondary organ dysfunctions in 611
  trait 609
Thanatophoric dwarfism 730
Therapeutic hypothermia 318
Thermometers 886
Thermoneutral environment 328
Thermoregulation in newborns 328
Thiamine (B1) deficiency 100
Thoracocentesis 438, 882
Threadworm, *see* Enterobiasis 257
Three-layer test 466
Three-way 873
Thrill, fluid 374
Thrombin time 621
Thrombopoiesis 598
Thrombopoietin 632
Thrombotic microangiopathy 665
Thrombotic thrombocytopenic purpura 624
Thrush 384
Thumb sign 449
Thumb-sucking 60
Thyroid
  crisis/storm 699
  disorders 695
  nodules 698
  storm 699

Tick typhus 208
Tics 61
Tinea versicolor 758
Tip-toe walking 725
Todd paralysis 553
Toddler's diarrhea 408
Tongue-tie 313
Torticollis 726
Total anomalous pulmonary venous drainage 506
Total parenteral nutrition 808
Touch therapy 311
Toxic epidermal necrolysis 767
Toxic-shock syndrome 178
Toxidromes 821
Toxocariasis 257
Trace elements 68
Tracheoesophageal fistula 385
Tracheostomy 796, 876
Tracheostomy tube 876
Trachoma 779
Trail sign 434
Transfusion associated circulatory overload 631
Transfusion-related acute lung injury 630
Transient erythroblastopenia 615
Transient hypogammaglobulinemia 136
Transient synovitis of hip 733
Transient tachypnea in newborn 335
Transition milk 69
Transitional stools 313
Transport of a sick newborn 315
Transport of sick child 794
Transposition of great arteries 505
Treacher Collins syndrome 383, 721
Tremors 556
Trendelenburg gait 728
Trendelenburg gait *see* Waddling gait
Trichorrhexis nodosa 773
Trichotillomania 773
Trichuriasis 257
Tricuspid atresia 506
Tricuspid regurgitation 514
Trigger thumbs/fingers 722
Trigonocephaly 720
Triple-bubble sign 392
Trivandrum development chart 24
Tropical pulmonary eosinophilia 254
  diagnostic criteria 254
Tropical pulmonary eosinophilia 465
Tropical sprue 406
True hermaphrodites 706
Trummerfeld zone of rarefaction 105
TT vaccine 149
Tubercular aortoarteritis 750
Tubercular dactylitis 734
Tuberculin sensitivity test 196
Tuberculosis
  diagnostic algorithm 193, 198
  drug resistant tuberculosis 198
  management 197
  natural history 190
  paradoxical upgrading reactions 200
  preventive therapy 200
  treatment interruptions 199
  treatment regimen 199
Tuberculosis, types 189
  abdominal 407
  clinically diagnosed 197
  congenital 200
  disseminated 192
  extensive pulmonary 192
  extrapulmonary 193
  genitourinary 687
  meningitis
  miliary 192
  osteoarticular 733
  presumptive pediatric 194
  primary complex 191
  probable TB 197
  pulmonary 192
  severe extrapulmonary 193
  skin 758
  tuberculoma 574
Tuberous sclerosis 578
  diagnostic criteria 579
Tubular disorders 677
  hereditary 679
Tumor
  androgen-producing 705
  Askin 649
  brain 575
  estrogen-producing 705
  lysis syndrome 638
  spinal cord 584
  testicular 690
  Wilms' 647
Turner syndrome 273
  clinical spectrum 273
  cytogenetics 273
  diagnosis 273
  prenatal diagnosis 273
Twin-to-twin transfusion 298
Typhoid fever, *see* Enteric fever
Typhoid vaccine 155
Typical myoclonic epilepsy of early childhood 548
Tyrosinemia 281

U

Ulcerative colitis 406
Umbilical
  bleeding 307
  discharge 307
  hernia 395
  sepsis 345
Under-5 mortality rate 2, 832
Under-fives' clinics 837
Undernutrition, *see* childhood undernutrition
Undescended testis, *see* Cryptorchidism
Uniparental disomy 269
Universal immunization program 162
Urea cycle defects 284
Urinary tract infections 685
  antibiotic therapy 687
  chronic or recurrent 686
  diagnosis
    laboratory 686
    presumptive 686
    rapid dipstick tests 686
  diagnostic indicators 686
  management 687
  predisposing factors 686
  prevention of recurrence 687
  prophylaxis 684
  types
    complicated 686
    uncomplicated 686
Urinary tract malformations 680, 681
Urine examination 655
Urticaria 763
Uterine bleeding in adolescents 367

V

Vaccine
  associated paralytic polio 151
  carrier 165
  derived polioviruses 151
  hesitancy 167
  storage in refrigerator 164
  vial monitor 165
Vaccines 146
  adjuvants 147
  conjugated 146
  contact immunity 146
  diluents 147
  herd effect 146
  inactivated 146
  live 146
  polysaccharide 146
  preservatives 147
  stabilizers 147
Vaccines at a glance 150
Vaginal
  bleeding in newborn 313
  discharge in adolescents 367
  discharge in newborn 313
Vaginosis, non-specific 367
Varicella vaccine 155
Varicocele 689
Vasculitis syndromes 747
Vaso-occlusive crises 613
Vasopressin-challenge test 694
VATER association 361
Ventilation, bag and mask 874
Ventricular septal defect 496
  course and complications 497
  hemodynamics 496
  management 497
Ventriculoperitoneal shunt 562
Ventriculostomy, endoscopic third 562
Vernix caseosa 306
Verruca vulgaris, *see* Common warts
Vesicoureteral reflux 683
  international classification 684
Vincent angina 207, 384
Vineland adaptive behavior scale 42, 44
Viral hepatitis 419
  hepatitis A 419
  hepatitis B 420
    chronic disease 425
    infants born to HbsAg positive mothers 421
    sero-markers 421
  hepatitis D 421
  hepatitis E 421
  hepatitis C 421
  hepatitis G 421
Visual epilepsy, childhood onset of 549
Vitamin (B6) deficiency 102
Vitamin A 98
Vitamin A deficiency 99

Vitamin B12 deficiency 606
Vitamin C 104
Vitamin C excess 105
Vitamin D 105
  metabolism 106
  physiology 105
Vitamin D resistant rickets 108
Vitamin D-dependent rickets 109
Vitamin E 109
Vitamin E deficiency 109
Vitamin K 109
Vitamin K deficiency 110
Vitiligo 761
Volpe's classification 318
Volvulus, *see* Malrotation
Vomiting 376
Vomiting in newborn 313
Vomiting, cyclic 378
von Gierke disease 287
von Willebrand disease 627
Von-Hippel Lindau disease 577

W

Waardenburg syndrome 782
Waddling (Trendelenburg) gait 592
Waddling gait 728
WAGR syndrome 647
Warm chain 330
Water homeostasis, body 114
Water homeostasis, body physiology 115
Water-deprivation test 694
Waterhouse-Friderichsen syndrome 187, 701
Wechsler intelligence scale for children 44
Wegener granulomatosis 748
Weighing scales 886
Weight, measurement 13
Welcome-trust classification 90
Werdnig-Hoffmann disease 587
Wernike's encephalopathy 102
West syndrome 548
Wheezers in childhood, phenotypes 455
Wheezing 441
Whipworm, *see* Trichuriasis
White line of Frankel 105
WHO child growth standards 12
whole genome sequencing 276
Whooping cough 182
  clinical stages 182
  complications 183
  diagnosis 183
  prevention 183
  treatment 183
WHO-ORS 398
  composition 399
  RESOMAL 399
  super ORS 399
Widal test 184
William syndrome 122, 272
Wilms tumor 647
  national staging system 647
Wilson disease 112, 426
Wimberger's ring sign 105
Wiskott-Aldrich syndrome 137, 624
Wolman disease 287

X

Xeroderma pigmentosum 765
Xerophthalmia, WHO classification 99
Xerostomia 385
X-linked dominant disorders 268
X-linked recessive disorders 267
Yellow fever vaccine 156
Yellow-nail syndrome 775

Z

Zellweger syndrome 285
Zinc 110
Zinc deficiency 110
Z-score 11

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